Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/009880

International filing date: 24 March 2005 (24.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/578,769
Filing date: 10 June 2004 (10.06.2004)

Date of receipt at the International Bureau: 02 May 2005 (02.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

1312688

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 22, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: ***60/578,769***
FILING DATE: ***June 10, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US05/09880***

UNITED STATES PATENT AND TRADEMARK OFFICE DEPARTMENT OF COMMERCE

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

16563 U.S.PTO 061004

Docket No.: 59527US003

Transmittal of Provisional Application

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Inventor(s): Larry R. Krepski, White Bear Lake, MN; Joseph F. Dellaria, Jr., Woodbury, MN; Daniel E. Duffy, White Bear Lake, MN; David T. Amos, St. Paul, MN; and Bernhard M. Zimmermann, Eagan, MN

Title: AMIDE SUBSTITUTED IMIDAZOPYRIDINES, IMIDAZOQUINOLINES, AND IMIDAZONAPHTHYRIDINES

17497 U.S. PTO 60/578769 061004

1. ☒ Enclosed is the above-identified new provisional application for patent under 35 USC § 111(b)(1). It includes:
   202 Pages of Text
   0 Sheets of Drawings
2. ☐ Enclosed is an executed Assignment to 3M Innovative Properties Company and a completed Assignment Recordation Cover Sheet.
3. ☐ This invention was made under a contract with an agency of the U.S. Government:
   Agency: ______
   Contract No. ______
4. ☒ Correspondence Address: Dean A. Ersfeld
   Office of Intellectual Property Counsel
   3M Innovative Properties Company
   P.O. Box 33427
   St. Paul, Minnesota 55133-3427
5. ☒ Please charge the $160.00 filing fee under 37 CFR § 1.16(k) to Deposit Account No. 13-3723. One copy of this sheet marked duplicate is also enclosed.
6. ☒ Please charge to Deposit Account No. 13-3723 any fees under 37 CFR §§ 1.16 and 1.17, which may be required to file and during the entire pendency of this application. This authorization includes the fee for any necessary extension of time under 37 CFR § 1.136(a). To the extent any such extension should become necessary, it is hereby requested.
7. ☒ Enclosed is a return receipt postcard.

Respectfully submitted,

10 June 2004
Date

By: Dean A. Ersfeld
Dean A. Ersfeld, Reg. No.: 46,689
Telephone No.: (651) 733-7830

Office of Intellectual Property Counsel
3M Innovative Properties Company
Facsimile No.: (651) 736-3833

Filing of Papers and Fees by Express Mailing	
Pursuant to 37 CFR § 1.10, this application and the documents and fees listed on this transmittal letter are being deposited on the date indicated below with the United States Postal Service "Express Mail Post Office to Addressee" service addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450	
Date of Deposit June 10, 2004	Express Mail Label No. EV454445471US

☒ Customer Number for
Correspondence Address: **32692**

Patent
Docket No. 59527US003

AMIDE SUBSTITUTED IMIDAZOPYRIDINES, IMIDAZOQUINOLINES, AND IMIDAZONAPHTHYRIDINES

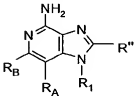
BACKGROUND OF THE INVENTION

There has been a major effort in recent years to find compounds that modulate the immune system. Examples of such compounds, which have demonstrated cytokine inducing and immunomodulating activity, are disclosed, for example, by U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,446,153; 5,482,936; 5,494,916; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,541,485; 6,545,016; 6,545,017; 6,656,938; 6,660,735; 6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372; 6,677,347; 6,677,348; and 6,683,088.

But despite important progress in the effort to find immunomodulating compounds, there is still a critical scientific and medical need for additional compounds that have an ability to modulate aspects of the immune response, by induction of cytokine biosynthesis or other mechanisms.

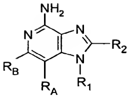
SUMMARY OF THE INVENTION

It has now been found that certain amide substituted imidazopyridine, imidazoquiniline, and imidazonaphthyridine compounds modulate cytokine biosynthesis. In one aspect, the present invention provides compounds of the Formula I:

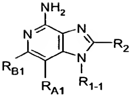


I

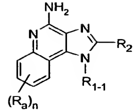
and more specifically the following compounds of the Formulas II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII:



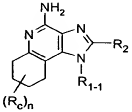
II



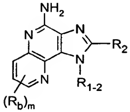
III



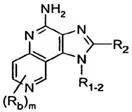
IV



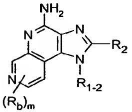
V



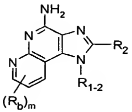
VI



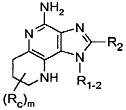
VII



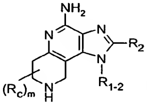
VIII



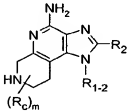
IX



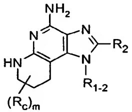
X



XI



XII



XIII

wherein R_1, $R_{1\text{-}1}$, $R_{1\text{-}2}$, R'', R_2, R_A, R_B, R_{A1}, R_{B1}, R_a, R_b, R_c, n and m are as defined below; and pharmaceutically acceptable salts thereof.

The compounds of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII are useful, for example, as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce or inhibit the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. Compounds can be tested, for example, using the test procedures described in the Examples Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human PBMC in a culture with the compound(s) at a concentration range of 30 to 0.014 μM and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. Compounds can be tested for inhibition of cytokine biosynthesis by incubating mouse macrophage cell line Raw 264.7 in a culture with the compound(s) at a

single concentration of, for example, 5 μM and analyzing for tumor necrosis factor (α) in the culture supernatant. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of inducing cytokine biosynthesis in animal cells, treating a viral disease in an animal, and/or treating a neoplastic disease in an animal by administering to the animal one or more compounds of the Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII, and/or pharmaceutically acceptable salts thereof.

In another aspect, the invention provides methods of synthesizing the compounds of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, and XIII and intermediates useful in the synthesis of these compounds.

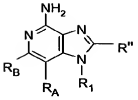
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive or exhaustive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides imidazopyridine, imidazoquinoline and imidazonaphthyridine compounds of the following Formula I:

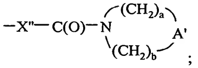


I

wherein:

R_1 is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

each R_a is independently selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

each R_b is independently selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

each R_c is independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_6 is independently selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl; and

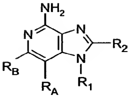
R" is hydrogen or a non-interfering substituent;

with the proviso that when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be $-X''-C(O)-N(R_1')(R_1'')$;

or a pharmaceutically acceptable salt thereof.

In some embodiments, compounds or salts of Formula I induce the biosynthesis of one or more cytokines.

The present invention also provides imidazopyridine, imidazoquinoline and imidazonaphthyridine compounds of the following Formula II:

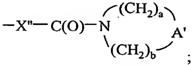


II

wherein:

R_1 is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

each R_a is independently selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

each R_b is independently selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

each R_c is independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

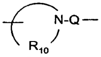
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

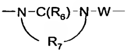
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

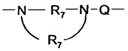
$-C(R_6)-N(OR_9)-$,



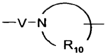
,



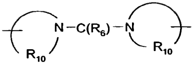
,



,



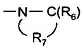
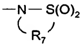
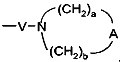
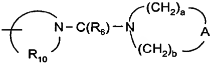
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

 ,  ,  , and  ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

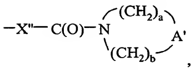
with the proviso that when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be $-X''-C(O)-N(R_1')(R_1'')$;

or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula II, X' is $-CH_2-C_{0-10}$ alkylene- or X'' is $-CH_2-C_{0-10}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

In some embodiments of Formula II, A' is -O- or $-N(Q-R_4)-$, and a and b are independently integers from 2 to 3; or A' is $-CH_2-$, and a and b are independently integers from 1 to 3.

In some embodiments of Formula II, R_1 is



, A' is -O- or $-N(Q-R_4)-$, and a and b are independently integers from 2 to 3; or A' is $-CH_2-$, and a and b are independently integers from 1 to 3.

In some embodiments of Formula II, R_1' is hydrogen or C_{1-3} alkyl.

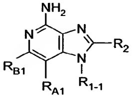
In some embodiments of Formula II, R_1'' is hydrogen.

In some embodiments of Formula II, R_1' and R_1'' are methyl.

In some embodiments of Formula II, R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl. In certain embodiments, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl.

In some embodiments of Formula II, the fused aryl ring, fused heteroaryl ring, fused 5 to 7 membered saturated ring, or fused 5 to 7 membered saturated ring containing one N or S atom is unsubstituted.

The present invention also provides imidazopyridine compounds of the following Formula III:

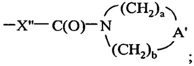


III

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_{A1} and R_{B1} are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is in selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

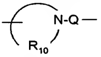
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

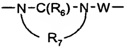
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

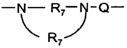
$-C(R_6)-N(OR_9)-$,



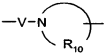
,



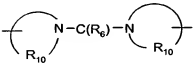
,



,



, and

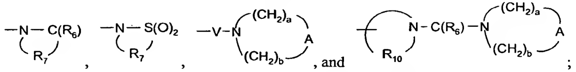


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents

independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

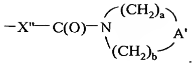
each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

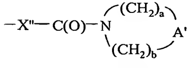
In some embodiments of Formula III, X' is $-CH_2-C_{0-4}$ alkylene- or X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-, and in certain embodiments, X' is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, or $-CH_2C(CH_3)_2CH_2-$; or X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

In some embodiments of Formula III, A' is -O-, and a and b are each 2.

In some embodiments of Formula III, R_{1-1} is



In some embodiments of Formula III, R_{1-1} is

 , A' is -O-, and a and b are each 2.

In some embodiments of Formula III, R_1' is hydrogen or C_{1-3} alkyl, and R_1" is hydrogen.

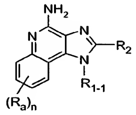
In some embodiments of Formula III, R_1' and R_1" are hydrogen.

In some embodiments of Formula III, R_1' and R_1" are methyl.

In some embodiments of Formula III, R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X-R_4, or -X-Y-R_4; X is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, or -C(R_6)-N(OR_9)-; and R_4 is alkyl. In certain embodiments, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl, and in certain other embodiments, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

In some embodiments of Formula III, R_{A1} and R_{B1} are methyl.

The present invention also provides imidazoquinoline compounds of the following Formula IV:

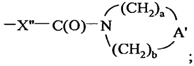


IV

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and

 ;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and

-CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, -CH_2-, -S(O)$_{0-2}$-, and

-N(Q-R_4)-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_a is independently selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and -N(R_9)$_2$;

n is an integer of 0 to 4;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

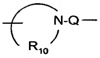
-O-C(O)-O-,

-N(R_8)-Q-,

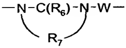
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

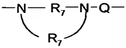
-C(R_6)-N(OR_9)-,



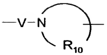
,

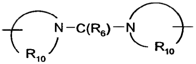


,



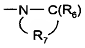
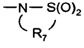
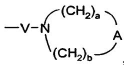
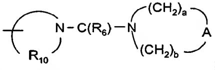
,

, and

;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

, , , and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

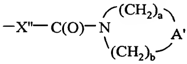
each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula IV, X' is $-CH_2-C_{0-4}$ alkylene- or X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-, and in certain embodiments, X' is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, or $-CH_2C(CH_3)_2CH_2-$; or X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

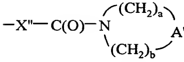
In some embodiments of Formula IV, A' is -O-, and a and b are each 2.

In some embodiments of Formula IV, R_{1-1} is



.

In some embodiments of Formula IV, R_{1-1} is



, A' is -O-, and a and b are each 2.

In some embodiments of Formula IV, R_1' is hydrogen or C_{1-3} alkyl, and R_1" is hydrogen.

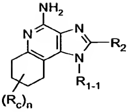
In some embodiments of Formula IV, R_1' and R_1" are hydrogen.

In some embodiments of Formula IV, R_1' and R_1" are methyl.

In some embodiments of Formula IV, R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$. $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl. In certain embodiments, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. In certain other embodiments, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

In some embodiments of Formula IV, n is 0.

The present invention also provides 6,7,8,9-tetrahydroimidazoquinoline compounds of the following Formula V:

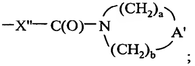


V

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_c is independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$;

n is an integer of 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,

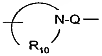
-O-C(O)-O-,

-N(R_8)-Q-,

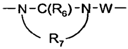
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

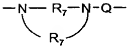
-C(R_6)-N(OR_9)-,



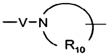
,



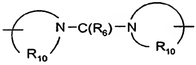
,



,



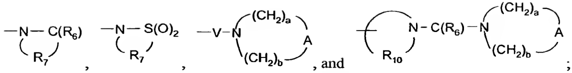
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

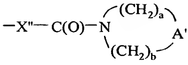
each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula V, X' is $-CH_2-C_{0-4}$ alkylene- or X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-. In certain embodiments, X' is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, or $-CH_2C(CH_3)_2CH_2-$; or X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

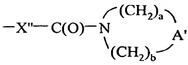
In some embodiments of Formula V, A' is -O-, and a and b are each 2.

In some embodiments of Formula V, R_{1-1} is



.

In some embodiments of Formula V, R_{1-1} is



, A' is -O-, and a and b are each 2.

In some embodiments of Formula V, R_1' is hydrogen or C_{1-3} alkyl, and R_1'' is hydrogen.

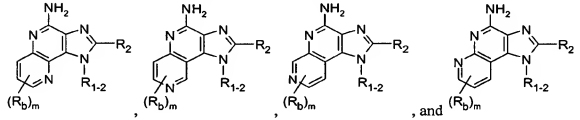
In some embodiments of Formula V, R_1' and R_1'' are hydrogen.

In some embodiments of Formula V, R_1' and R_1'' are methyl.

In some embodiments of Formula V, R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl. In certain embodiments, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. In certain other embodiments, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

In some embodiments of Formula V, n is 0.

The present invention also provides imidazonaphthyridine compounds selected from the group consisting of the following Formulas VI, VII, VIII, and IX:

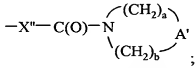


VI VII VIII IX

wherein:

R_{1-2} is selected from the group consisting of:

$-X''-C(O)-N(R_1')(R_1'')$ and



;

X'' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_b is independently selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

m is an integer of 0 to 3;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

-X-Y-R_4, and

-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

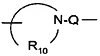
-O-C(O)-O-,

-N(R_8)-Q-,

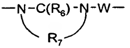
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

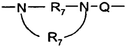
-C(R_6)-N(OR_9)-,



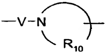
,



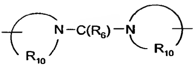
,



,



, and

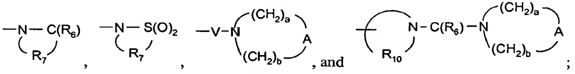


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

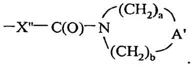
each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

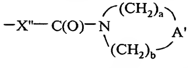
In some embodiments of Formulas VI, VII, VIII, and IX, X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-. In some embodiments, X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

In some embodiments of Formulas VI, VII, VIII, and IX, A' is -O-, and a and b are each 2.

In some embodiments of Formulas VI, VII, VIII, and IX, R_{1-2} is



In some embodiments of Formulas VI, VII, VIII, and IX, R_{1-2} is



, A' is -O-, and a and b are each 2.

In some embodiments of Formulas VI, VII, VIII, and IX, R_1' is hydrogen or C_{1-3} alkyl, and R_1" is hydrogen.

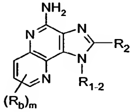
In some embodiments of Formulas VI, VII, VIII, and IX, R_1' and R_1" are hydrogen.

In some embodiments of Formulas VI, VII, VIII, and IX, R_1' and R_1" are methyl.

In some embodiments of Formulas VI, VII, VIII, and IX, R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl. In certain embodiments, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. In certain other embodiments, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

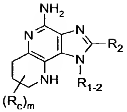
In some embodiments of Formulas VI, VII, VIII, and IX, m is 0.

In some embodiments the imidazonaphthyridine compounds are of the following Formulas VI:

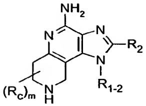


VI.

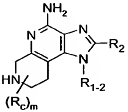
The present invention also provides 6,7,8,9-tetrahydroimidazonaphthyridine compounds selected from the group consisting of the following Formulas X, XI, XII, and XIII:



,

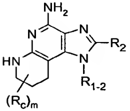


,



, and

X XI XII

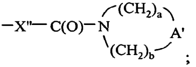


XIII

wherein:

R_{1-2} is selected from the group consisting of:

-X"-C(O)-N(R_1')(R_1") and



;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_c is independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$;

m is an integer of 0 to 3;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

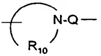
-O-C(O)-O-,

-N(R_8)-Q-,

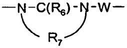
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

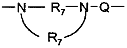
-C(R_6)-N(OR_9)-,



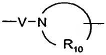
,



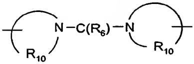
,



,



, and

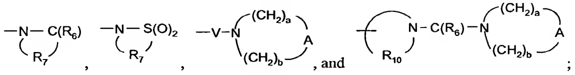


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy,

arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

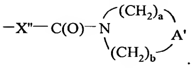
each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

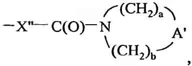
In some embodiments of Formulas X, XI, XII, and XIII, X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-. In certain embodiments, X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

In some embodiments of Formulas X, XI, XII, and XIII, A' is -O-, and a and b are each 2.

In some embodiments of Formulas X, XI, XII, and XIII, R_{1-2} is



In some embodiments of Formulas X, XI, XII, and XIII, R_{1-2} is



, A' is -O-, and a and b are each 2.

In some embodiments of Formulas X, XI, XII, and XIII, R_1' is hydrogen or C_{1-3} alkyl, and R_1'' is hydrogen.

In some embodiments of Formulas X, XI, XII, and XIII, R_1' and R_1'' are hydrogen.

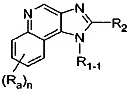
In some embodiments of Formulas X, XI, XII, and XIII, R_1' and R_1'' are methyl.

In some embodiments of Formulas X, XI, XII, and XIII, R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl. In certain embodiments, R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl. In certain other embodiments, R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

In some embodiments of Formulas X, XI, XII, and XIII, m is 0.

The present invention also provides compounds that are useful as intermediates in the synthesis of compounds of Formulas I-XIII. These intermediate compounds include those having the structural Formulas XIV, XV, and XVI described below.

The present invention provides intermediate compounds of the following Formula XIV:

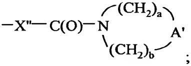


XIV

wherein:

R_{1-1} is selected from the group consisting of:

$-X'-C(O)-N(R_1')(R_1'')$ and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_a is independently selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

n is an integer of 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

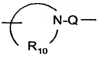
-O-C(O)-O-,

$-N(R_8)-Q-$,

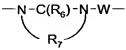
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

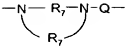
$-C(R_6)-N(OR_9)-$,

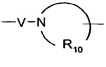


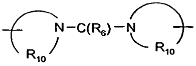
,



,

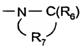
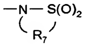
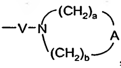
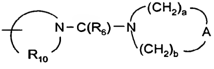

,


, and


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


,

,

, and

;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$,

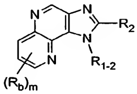
$-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

The present invention provides intermediate compounds of the following Formula XV:

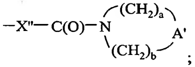


XV

wherein:

R_{1-2} is selected from the group consisting of:

$-X''-C(O)-N(R_1')(R_1'')$ and



;

X'' is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_b is independently selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and $-N(R_9)_2$;

m is an integer of 0 to 3;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

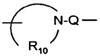
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

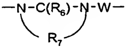
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

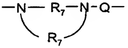
$-C(R_6)-N(OR_9)-$,



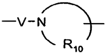
,



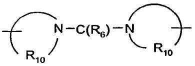
,



,



, and

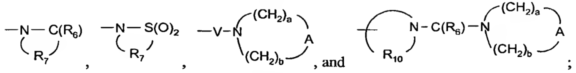


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents

independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

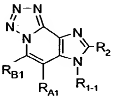
each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

The present invention provides intermediate compounds of the following Formula XVI:

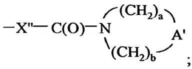


XVI

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_{A1} and R_{B1} are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is in selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

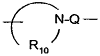
-O-C(O)-O-,

-N(R_8)-Q-,

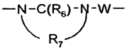
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

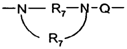
-C(R_6)-N(OR_9)-,



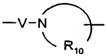
,



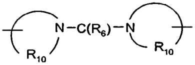
,



,



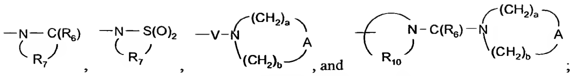
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the ability of the compound or salt to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R" groups include those described above for R_2 in Formulas II-XIV.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl,

cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. The terms "alkylenyl," "alkenylenyl," and "alkynylenyl" are used when "alkylene", "alkenylene:, and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an "alkylene" moiety to which an aryl group is attached.

The term “haloalkyl” is inclusive of alkyl groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix “halo-”. Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term “aryl” as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, homopiperazinyl, and the like.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group or substituent is present more that once in any Formula described herein, each group or substituent is independently selected, whether specifically stated or not.

The invention is inclusive of the compounds described herein and salts thereof in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Preparation of the Compounds

Compounds of Formula IVa can be prepared according to Reaction Scheme I, wherein R_a and n are as defined above, X_a is either X' or X", and R_{1-1a} and R_{2a} are subsets of R_{1-1} and R_2 as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to oxidation in step (5). These substituents include -S- and heteroaryl groups. In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline of Formula XX is reacted with an amino ester of the Formula H_2N-X_a-C(O)-O-alkyl or a hydrochloride salt thereof to form a compound of Formula XXI. This reaction is conveniently carried out by adding a compound of the Formula H_2N-X_a-C(O)-O-alkyl - HCl to a solution of a 4-chloro-3-nitroquinoline of Formula XX in the presence of a base such as triethylamine, potassium carbonate, or a combination thereof. The reaction is carried out in a suitable solvent, such as dichloromethane or chloroform. Compounds of the Formula H_2N-X_a-C(O)-O-alkyl - HCl can be commercially obtained or readily synthesized using conventional methods. For example, the amino ester wherein -alkyl is ethyl and X_a is butylene or dodecylene can be synthesized according to the procedure of C. Temple et al., *J. Med. Chem.*, *31*, pp. 697-700 (1988). Many compounds of Formula XX are known or can be prepared using known synthetic methods, see for example, U.S. Patent Nos. 4,689,338; 5,175,296; 5,367,076; and 5,389,640; and the documents cited therein.

The resultant compound of Formula XXI can be reduced in step (2) of Reaction Scheme I using a variety of methods to provide a quinoline-3,4-diamine of Formula XXII. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a

Parr apparatus in a suitable solvent such as toluene or ethanol. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

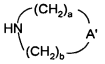
Alternatively step (2) can be carried out using a one- or two-phase sodium dithionite reduction. The reaction is conveniently carried out using the conditions described by Park, K. K.; Oh, C. H.; and Joung, W. K.; *Tetrahedron Lett.*, *34*, pp. 7445-7446 (1993) by adding sodium dithionite to a compound of Formula XXI in a mixture of dichloromethane and water at ambient temperature in the presence of potassium carbonate and ethyl viologen dibromide, ethyl viologen diiodide, or 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme I, a quinoline-3,4-diamine of Formula XXII is treated with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII. Suitable carboxylic acid equivalents include orthoesters of Formula $R_{2a}C(O\text{-alkyl})_3$, 1,1-dialkoxyalkyl alkanoates of Formula $R_{2a}C(O\text{-alkyl})_2(O\text{-}C(O)\text{-alkyl})$, and acid chlorides of Formula $R_{2a}C(O)Cl$. The selection of the carboxylic acid equivalent is determined by the desired substituent at R_{2a}. For example, triethyl orthoformate will provide a compound where R_{2a} is hydrogen, and trimethyl orthovalerate will provide a compound where R_{2a} is a butyl group. The reaction is conveniently carried out by adding the carboxylic acid equivalent to a quinoline-3,4-diamine of Formula XXII in a suitable solvent such as toluene. Optionally, catalytic pyridine hydrochloride or pyridium *p*-toluenesulfonate can be added. The reaction is carried out at a temperature high enough to drive off alcohol or water formed during the reaction. Conveniently, a Dean-Stark trap can be used to collect the volatiles.

Alternatively, step (3) can be carried out in two steps when an acid chloride of Formula $R_{2a}C(O)Cl$ is used as the carboxylic acid equivalent. The first step is conveniently carried out by adding the acid chloride to a solution of a quinoline-3,4-diamine of Formula XXII in a suitable solvent such as dichloromethane to afford an amide. Optionally, a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine can be added. The reaction can be carried out at ambient temperature. The amide product can be isolated and optionally purified using conventional techniques before it is heated and cyclized to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII. The cyclization reaction is conveniently carried out in a solvent such as ethanol or methanol in the presence of a base such as triethylamine and

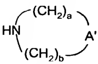
may be carried out at an elevated temperature, such as the reflux temperature of the solvent. The 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII can be isolated using conventional methods.

In step (4) or steps (4a) and (4b) of Reaction Scheme I, the ester group of a 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII is converted to an amide to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIVa. The transformation can be carried out by base-promoted hydrolysis of the ester in step (4a) to form a carboxylic acid of Formula XXIV. In step (4b), a carboxylic acid of Formula XXIV is converted to an acid chloride using conventional methods and then treated with an amine to provide an amide-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XIVa. The base-promoted hydrolysis in step (4a) is conveniently carried out by adding sodium hydroxide to an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods. The conversion of the resulting carboxylic acid to an acid chloride is conveniently carried out by slowly adding oxalyl chloride to a solution of the carboxylic acid in a suitable solvent such as dichloromethane. The reaction can be carried out at a sub-ambient temperature, such as 0 °C, or at ambient temperature. The resulting acid chloride can then be treated with an amine of Formula $HN(R_1')(R_1'')$ or

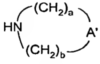


in a suitable solvent such as dichloromethane. Numerous amines of these formulas are commercially available; others can be prepared by known synthetic methods. The reaction can be run at ambient temperature, and the product of Formula XIVa or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, step (4) can be carried out in one step by treating an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII with an amine of Formula $HN(R_1')(R_1'')$ or

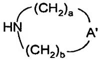
 or a hydrochloride salt thereof in the presence of trimethylaluminum. The reaction is conveniently carried out by adding a solution of an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXIII in a suitable solvent such

as dichloromethane to a pre-reacted mixture of trimethylaluminum and an amine of Formula HN(R_1')(R_1") or



or a hydrochloride salt thereof in a suitable solvent such as dichloromethane. The reaction can then be heated at an elevated temperature, for example, the reflux temperature of the solvent. The product can be isolated using conventional methods.

Step (4) of Reaction Scheme I can also be carried out by heating an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII in the presence of an amine of Formula HN(R_1')(R_1") or



at an elevated temperature such as 90-120 °C. The reaction is conveniently carried out in a high-pressure vessel and can be run neat or in a suitable solvent such as tetrahydrofuran (THF). An ester of Formula XXIII can be heated in the presence of ammonium acetate at an elevated temperature such as 110 to 140 °C to provide a compound of Formula XIVa, where

R_{1-1a} is -X'-C(O)-NH_2. The product can be isolated by conventional methods.

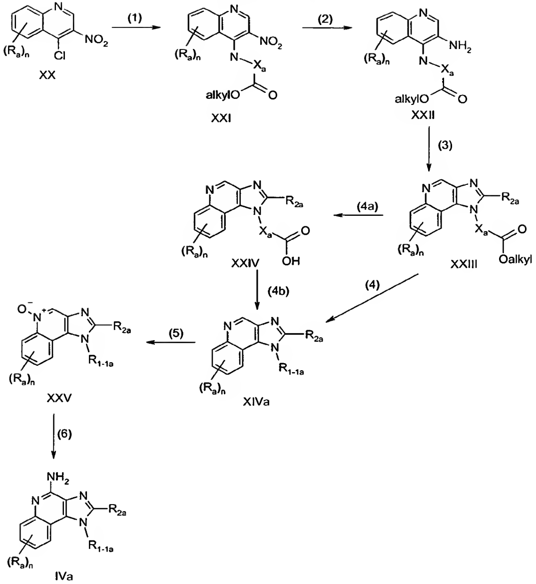
In step (5) of Reaction Scheme I, an amide-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XIVa is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXV using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XIVa in a solvent such as dichloromethane or chloroform. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (6) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXV is aminated to provide an amide-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula IVa. Step (6) can be carried out by the activation of an *N*-oxide of Formula XXV by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride.

Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XXV in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

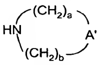
Steps (5) and (6) of Reaction Scheme I may be carried out as a one-pot procedure by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XIVa in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride without isolating the *N*-oxide compound of Formula XXV. The product of Formula IVa or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme I



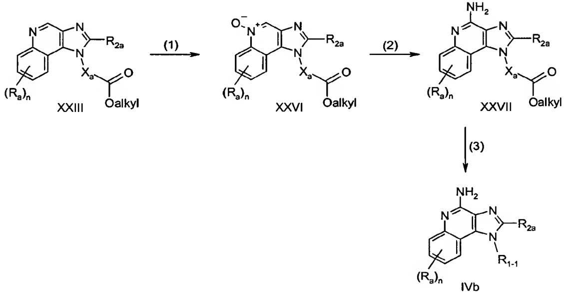
Compounds of the invention can also be prepared according to Reaction Scheme II, wherein R_a, R_{2a}, R_{1-1}, X_a, and n are as defined above. In step (1) of Reaction Scheme II, an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXIII is oxidized to an *N*-oxide of Formula XXVI, which is then aminated in step (2) to provide an ester-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine Formula XXVII. Steps (1) and (2) of Reaction Scheme II can be carried out as described for steps (5) and (6) of Reaction Scheme I.

In step (3) of Reaction Scheme II, an ester-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine Formula XXVII is heated in the presence of an amine of Formula $HN(R_1')(R_1'')$ or



at an elevated temperature such as 90-120 °C to provide an amide-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine Formula IVb. The reaction is conveniently carried out in a high-pressure vessel and can be run neat or in a suitable solvent such as tetrahydrofuran (THF). An ester of Formula XXVII can be heated in the presence of ammonium acetate at an elevated temperature such as 110 to 140 °C to provide a compound of Formula IVb, where $R_{1\text{-}1}$ is $-X_a\text{-}C(O)\text{-}NH_2$. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

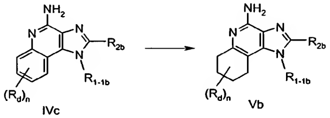
Reaction Scheme II



Compounds of the invention can also be prepared according to Reaction Scheme III, wherein R_d is alkyl, alkoxy, or $-N(R_9)_2$ and R_{2b} and $R_{1\text{-}1b}$ are subsets of R_2 and $R_{1\text{-}1}$ as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

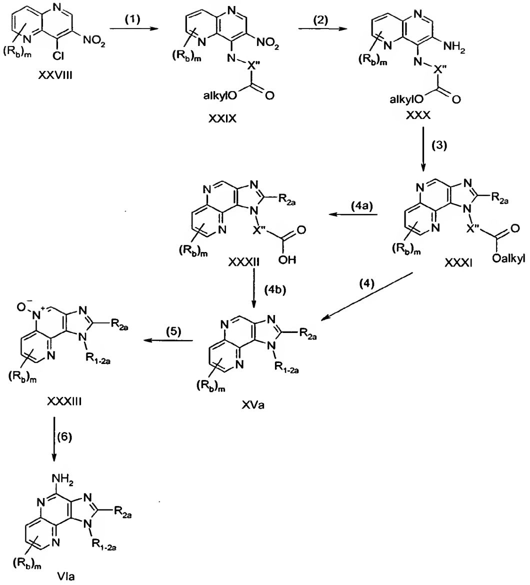
As shown in Reaction Scheme III, an 1*H*-imidazo[4,5-*c*]quinoline of Formula IVc can be reduced to a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Vb. The reaction is conveniently carried out under hetereogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula IVc in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme III



Compounds of the invention can be prepared according to Reaction Scheme IV, wherein R_b, X", R_{2a} and m are as defined above and R_{1-2a} is a subset of R_{1-2} as defined above that does not include those substituents that one skilled in the art would recognize as being susceptible to oxidation in step (5). These substituents include -S- and heteroaryl groups. Reaction Scheme IV begins with a 4-chloro-3-nitro[1,5]naphthyridine of Formula XXVIII. Compounds of Formula XXVIII and their preparation are known; see, for example, U.S. Patents Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster). Steps (1) through (6) of Reaction Scheme IV can be carried out as described for the corresponding steps (1) through (6) of Reaction Scheme I to provide an amide-substituted 1H-imidazo[4,5-c][1,5]naphthyridin-4-amine of Formula VIa. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme IV



For some embodiments, compounds of the invention are prepared according to Reaction Scheme V, where R_{1-1}, R_2, R_{A1}, R_{B1}, and X_a are as defined above and Ph is phenyl. In step (1) of Reaction Scheme V, a 2,4-dichloro-3-nitropyridine of Formula XXXIV is reacted with an amino ester of the Formula H_2N-X_a-C(O)-O-alkyl or a hydrochloride salt thereof to form a 2-chloro-3-nitropyridine of Formula XXXV. The reaction is conveniently carried out by combining an amino ester of Formula H_2N-X_a-C(O)-O-alkyl - HCl and a 2,4-dichloro-3-nitropyridine of Formula XXXIV in the presence

of a base such as triethylamine in an inert solvent such as *N,N*-dimethylformamide (DMF). The reaction can be carried out at ambient temperature, and the product can be isolated from the reaction mixture using conventional methods. Many 2,4-dichloro-3-nitropyridines of the Formula XXXIV are known and can be readily prepared using known synthetic methods. (See, for example, Dellaria et al, U.S. Pat. No. 6,525,064 and the references cited therein.)

In step (2) of Reaction Scheme V a 2-chloro-3-nitropyridine of Formula XXXV is reacted with an alkali metal azide to provide an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XXXVI. The reaction can be carried out by combining the compound of Formula XXXV with an alkali metal azide, for example, sodium azide, in a suitable solvent such as acetonitrile/water, preferably 90/10 acetonitrile/water, in the presence of cerium III chloride, preferably cerium III chloride heptahydrate. Optionally, the reaction can be carried out with heating, for example, at the reflux temperature. Alternatively, the reaction can be carried out by combining the compound of Formula XXXV with an alkali metal azide, for example, sodium azide, in a suitable solvent such as DMF and heating, for example to about 50-60 °C, optionally in the presence of ammonium chloride. The product can be isolated from the reaction mixture using conventional methods.

In step (3) of Reaction Scheme V, an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XXXVI is reduced to provide a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula XXXVII. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst, for example, platinum on carbon or palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as acetonitrile or ethyl acetate. The product can be isolated from the reaction mixture using conventional methods. Alternatively, the reduction can be carried out using the one- to two-phase sodium dithionite reduction described in step (2) of Reaction Scheme I.

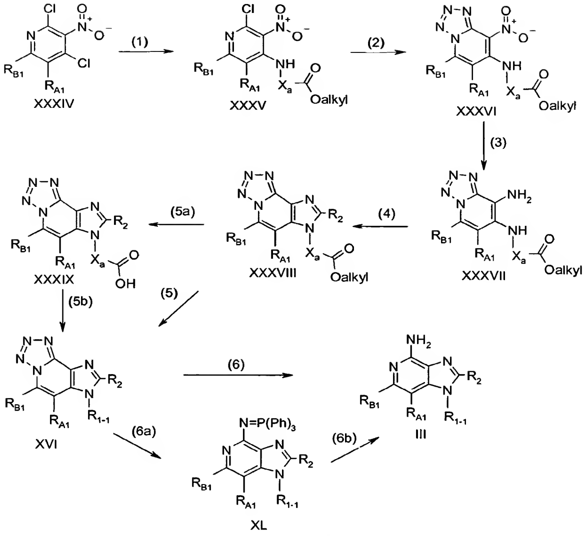
In step (4) of Reaction Scheme V, a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula XXXVII is reacted with a carboxylic acid equivalent to provide a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXXVIII. The reaction can be carried out as described in step (3) of Reaction Scheme I, and the product can be isolated from the reaction mixture using conventional methods.

In step (5) or steps (5a) and (5b) of Reaction Scheme V, the ester group of a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXXVIII is converted to an amide to provide an amide-substituted 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVI. The reaction can be carried out as described in step (4) or steps (4a) and (4b) of Reaction Scheme I, and the product can be isolated by conventional methods.

In step (6) of Reaction Scheme V, the tetrazolo ring is reductively removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of the Formula XVI to provide an amide-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of the Formula III or a pharmaceutically acceptable salt thereof. The reaction can be carried out by reacting the 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVI with hydrogen in the presence of a catalyst and an acid. The hydrogenation can be conveniently run at ambient temperature on a Parr apparatus with a suitable catalyst, such as platinum IV oxide, and a suitable acid, such as trifluoroacetic acid. The product or pharmaceutically acceptable salt thereof can be isolated from the reaction mixture using conventional methods.

Alternatively, the tetrazolo ring can be removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVI as shown in step (6a) by reaction with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate of Formula XL. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature. In step (6b) of Reaction Scheme V an *N*-triphenylphosphinyl intermediate of Formula XL is hydrolyzed to provide an amide-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula III. The hydrolysis can be carried out by general methods well known to those skilled in the art, for example, by heating in a lower alkanol in the presence of an acid. The product can be isolated from the reaction mixture using conventional methods as the compound of Formula III or as a pharmaceutically acceptable salt thereof.

Reaction Scheme V

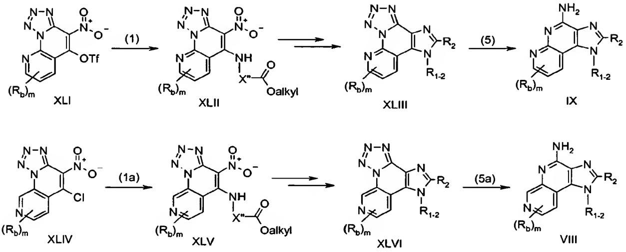


For some embodiments, naphthyridines of the invention are prepared from tetrazolo compounds of Formulas XLI and XLIV according to Reaction Scheme VI, wherein R_{1-2}, R_2, R_b, m, and X" are as defined above and -OTf is a trifluoromethanesulfonate group. Compounds of Formula XLI and XLIV and synthetic routes to these compounds are known; see, for example, U.S. Patent Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster).

In steps (1) and (1a) of Reaction Scheme VI, a tetrazolonaphthyridine of Formula XLI or XLIV is reacted with an amino ester of the Formula H_2N-X_a-C(O)-O-alkyl or a hydrochloride salt thereof to form a compound of Formula XLII or XLV. The reaction

can be carried out as described in step (1) of Reaction Scheme I. An ester-substituted tetrazolonaphthyridine of Formula XLII or XLV is converted to a compound of Formula XLIII or XLVI according to the methods of steps (2), (3), and (4) or (4a) and (4b) of Reaction Scheme I. The tetrazolo group of a compound of Formula XLIII or XLVI can then be removed to provide a 1*H*-imidazo[4,5-*c*]naphthyridin-4-amine of Formula IX or VIII. The removal of the tetrazolo group can be carried out as described in step (6) or steps (6a) and (6b) of Reaction Scheme V or by methods described in U.S. Patent Nos. 6,194,425 (Gerster) and 6,518,280 (Gerster). The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme VI



Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The term “a therapeutically effective amount” or "effective amount" means an amount of the compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the

physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg, of the compound to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds of the invention have been shown to modulate (e.g., induce) the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. The animal to which the compound or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound may provide therapeutic treatment. Alternatively, the compound may be administered to the animal prior to the animal acquiring the disease so that administration of the compound may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds of the invention may affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. Certain compounds may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, certain compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of certain compounds.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus,

Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection; and

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, renal cell carcinoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers; and

(e) T_H2-mediated, atopic, and autoimmune diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, Ommen's syndrome, discoid lupus, alopecia areata, inhibition of keloid formation and other types of scarring, and enhancing would healing, including chronic wounds.

IRMs identified herein also may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; recombinant proteins; glycoproteins; peptides; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

IRMs may also be particularly helpful in individuals having compromised immune function. For example, IRM compounds may be used for treating the opportunistic

infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of Formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, or XIII to the animal.

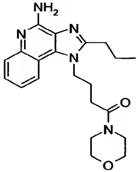
An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Example 1

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one



Part A

Ethanol (500 mL) was cooled to 0 °C, and thionyl chloride (85 mL, 1.2 mol) was added dropwise with stirring. The reaction was stirred for one hour at 0 °C, and solid 4-aminobutyric acid (100 g, 0.97 mol) was then added. After ten minutes of stirring, the reaction was allowed to warm to ambient temperature and stirred for two hours. The reaction was then allowed to stand at ambient temperature overnight. The ethanol was removed under reduced pressure, and the solid residue was dissolved in ethyl acetate. After one hour, the solution was cooled to 0 °C, and a precipitate formed. The precipitate was isolated by filtration and washed with diethyl ether (300 mL) to provide 126.6 g of ethyl 4-aminobutyrate hydrochloride as a white solid. A precipitate formed in the filtrate and was isolated by filtration to provide 19.1 g of ethyl 4-aminobutyrate hydrochloride as a white solid.

Part B

Triethylamine (50.0 mL, 358 mmol) and potassium carbonate (40 g, 290 mmol) were added to a solution of 4-chloro-3-nitroquinoline (49.6 g, 238 mmol) in tetrahydrofuran (THF) (100 mL) and chloroform (250 mL). Ethyl 4-aminobutyrate hydrochloride (43.8 g, 262 mmol) was added in portions over a period of five minutes during which time an ice bath was used to cool the reaction. The reaction was stirred with cooling for 30 minutes, allowed to warm to ambient temperature, and stirred overnight. An analysis by thin layer chromatography (TLC) indicated the presence of 4-chloro-3-nitroquinoline. Additional ethyl 4-aminobutyrate hydrochloride (8.0 g, 48 mmol) was added, and the reaction was stirred at ambient temperature for one hour and then heated at reflux for two hours. Additional triethylamine (20 mL) was added, and the reaction was

heated at reflux for one hour, cooled to ambient temperature, washed with water (3 x 100 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 63.8 g of ethyl 4-(3-nitroquinolin-4-ylamino)butyrate as a yellow solid.

Part C

A mixture of ethyl 4-(3-nitroquinolin-4-ylamino)butyrate (20.0 g, 65.9 mmol), 10% palladium on carbon (0.50 g), and ethanol (250 mL) was added to a Parr vessel, and the reaction was placed under hydrogen pressure (43 psi, 3.0×10^5 Pa) for 3.5 hours. The pressure decreased to 31 psi (2.1×10^5 Pa) during the reaction. The reaction mixture was filtered through a layer of CELITE filter agent, and the filtrate was concentrated under reduced pressure.

Part D

Trimethyl orthobutyrate (10.4 g, 70.2 mmol) and pyridinium *p*-toluenesulfonate (0.25 g, 1.0 mmol) were added to a solution of the material from Part C in toluene (350 mL), and the reaction was heated at reflux under a Dean-Stark trap for three hours while the distillate was periodically removed. The toluene was removed under reduced pressure, and the residue was stirred with 70:30 hexanes:ethyl acetate (75 mL). Additional hexane (50 mL) was added to form a precipitate. The supernatant liquid was decanted away to afford 6.75 g of a brown solid, which was mixed with 20.8 g of material from another run. The crude product was then purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) to provide 14.2 g of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate as an oil that crystallized upon standing.

Part E

Trimethylaluminum (available as a 2 M solution in toluene, 15.5 mL, 31.0 mmol) was added dropwise with stirring to a solution of morpholine (2.7 mL, 31 mmol) in dichloromethane (75 mL) at ambient temperature. After 20 minutes, a solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate (5.0 g, 15 mmol) in dichloromethane (15 mL) was added dropwise. The reaction was then heated at reflux for three days. An analysis by high-performance liquid chromatography (HPLC) indicated the presence of starting material, and additional morpholine (0.2 mL) was added. The reaction was heated at reflux for three hours and then allowed to stand at room temperature over three days. Hydrochloric acid (4 mL of 10%) was slowly added followed by saturated aqueous sodium bicarbonate (8 mL). The organic layer was decanted away from solids formed

during the reaction. The solids were extracted with dichloromethane (2 x 50 mL), and the combined organic fractions were washed with 5% aqueous sodium hydroxide (35 mL) and saturated aqueous sodium bicarbonate (35 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide a light yellow solid.

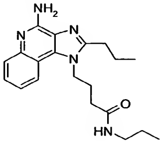
Part F

3-Chloroperoxybenzoic acid (mCPBA) (available as 77% pure material, 8.5 g, 38 mmol) was added in portions over a period of two minutes to a solution of the material from Part E in dichloromethane (100 mL), and the reaction was stirred for 45 minutes at ambient temperature and then washed with 5% aqueous sodium hydroxide (2 x 35 mL) and water (25 mL). Concentrated ammonium hydroxide (100 mL of 29%) and *p*-toluenesulfonyl chloride (4.9 g, 26 mmol) were then sequentially added with vigorous stirring, and the reaction was stirred for 30 minutes. The aqueous layer was separated and extracted with dichloromethane (4 x 50 mL). The combined organic fractions were washed with 5% aqueous sodium hydroxide solution (2 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The residue was recrystallized twice from acetonitrile (15 mL) and methanol (4 mL) to provide 0.96 g of a light orange solid. A portion was dried overnight in a vacuum oven to provide 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one as a light yellow needles, mp 200-202 °C.

Anal. Calcd for $C_{21}H_{27}N_5O_2$: C, 66.12; H, 7.13; N, 18.36. Found: C, 65.86; H, 7.39; N, 18.21.

Example 2

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylbutyramide



Part A

A solution of *n*-propylamine (3.0 mL, 36 mmol) in dichloromethane (75 mL) was cooled to 0 °C; trimethylaluminum (available as a 2 M solution in toluene, 18 mL, 36 mmol) was added dropwise with stirring over a period of three minutes. The reaction was stirred for one hour at 0 °C and 30 minutes at ambient temperature. A solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate (5.80 g, 17.8 mmol, prepared as described in Parts A-D of Example 1) in dichloromethane (30 mL) was added, and the reaction was then heated at reflux for three days. The work-up procedure described in Part E of Example 1 was followed to provide *N*-propyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide as a brown oil.

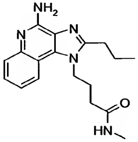
Part B

N-Propyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide (5.6 g, 15 mmol) was treated with mCPBA (8.5 g, 38 mmol), concentrated ammonium hydroxide (100 mL), and *p*-toluenesulfonyl chloride (4.9 g, 26 mmol) according to the method described in Part F of Example 1. The crude product was dissolved in hot toluene (25 mL) and dichloromethane. A precipitate slowly formed, was isolated by filtration, and was washed with toluene (15 mL). The solid was recrystallized twice from 4:1 methanol:water (25 mL), and the crystals were heated at reflux in chloroform in the presence of charcoal (1 g). The mixture was filtered through a layer of CELITE filter agent, and the filtrate was concentrated under reduced pressure. The residue was recrystallized twice from methanol:water and twice from toluene (15 mL) and dried overnight in a vacuum oven to provide 0.74 g of 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylbutyramide as a grey solid, mp 161-163 °C.

Anal. Calcd for $C_{20}H_{27}N_5O$: C, 67.96; H, 7.70; N, 19.81. Found: C, 67.64; H, 7.92; N, 19.83.

Example 3

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylbutyramide



Part A

A suspension of 4-chloro-3-nitroquinoline (75.0 g, 0.360 mol) in chloroform (400 mL) was cooled to 0 °C; triethylamine (75 mL, 0.54 mol) was added. Ethyl 4-aminobutyrate hydrochloride (66.0 g, 0.390 mol), prepared as described in Part A of Example 1, was added in portions over a period of five minutes. The reaction was stirred at 0 °C for 1 hour, allowed to warm to ambient temperature, and stirred overnight. An analysis by thin layer chromatography (TLC) indicated the presence of 4-chloro-3-nitroquinoline. Additional triethylamine (15 mL) was added, and the reaction was stirred for one hour. Additional ethyl 4-aminobutyrate hydrochloride (10.0 g) was added, and the reaction was heated at reflux for five hours. Additional triethylamine (22 mL) was added, and the reaction was stirred overnight at ambient temperature and heated at reflux for one hour. An analysis by TLC indicated the reaction was complete. The reaction was cooled to ambient temperature and washed with water (5 x 400 mL), and the resulting solution was used in Part B.

Part B

Chloroform was added to the material from Part A to provide a volume of 750 mL. Water (600 mL), potassium carbonate (80 g, 0.6 mol), and 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide (0.50 g, 0.92 mmol) were added. Sodium hydrosulfite (available as 85% pure material, 120 g, 0.68 mol) was then added in portions over a period of one hour, and the reaction was stirred at ambient temperature for three days. The reaction was not complete as evidenced by an HPLC analysis. Additional sodium hydrosulfite (20 g), potassium carbonate (20 g), and 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide (0.25 g) were added, and the reaction was stirred for three hours. Additional sodium hydrosulfite (20 g), potassium carbonate (20 g), and water (200 mL) were added, and the reaction was stirred

overnight. Additional sodium hydrosulfite (5 g) and potassium carbonate (5 g) were added, and the reaction was stirred for three hours. Additional sodium hydrosulfite (5 g) was added, and the reaction was stirred for two hours. An analysis by TLC indicated the reaction was complete. The organic layer was separated and washed with water (5 x 200 mL), dried over potassium carbonate, and concentrated under reduced pressure to provide 97.4 g of 4-(3-aminoquinolin-4-ylamino) ethyl butyrate as a dark oil.

Part C

A solution of 4-(3-aminoquinolin-4-ylamino) ethyl butyrate (72.0 g, 263 mmol) in toluene (700 mL) was heated at reflux for 10 minutes and then cooled slightly. Trimethyl orthobutyrate (42 g, 280 mmol) and pyridinium *p*-toluenesulfonate (1.0 g, 4.0 mmol) were added, and the reaction was heated at reflux under a Dean-Stark trap for two hours while the distillate was periodically removed. The reaction was then stirred overnight at ambient temperature. Charcoal (5 g) was added, and the resulting mixture was heated at reflux for three hours and then filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure to provide an oil that crystallized upon standing. The solid was dissolved in hot methanol (125 mL), and water (50 mL) was added. After one hour, the mixture was cooled in an ice bath to form a precipitate. The precipitate was isolated by filtration and dissolved in dichloromethane. A layer of water was present and was removed. The remaining solution was dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 53.2 g of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate.

Part D

A mixture of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate (2.0 g, 6.1 mmol), THF (10 mL), and methylamine (available as a 40% solution in water, 4 mL, 52 mmol) was sealed in a high-pressure vessel and heated at 70 °C overnight. An analysis by TLC indicated the presence of starting material, and the reaction was sealed and heated at 80 °C for nine hours. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (100 mL). The resulting solution was washed with 5% aqueous sodium hydroxide (2 x 25 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 1.83 g of *N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide.

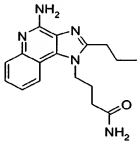
Part E

mCPBA (3.3 g, 15 mmol) was added to a solution of *N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide (1.83 g, 5.90 mmol) in chloroform (75 mL), and the reaction was stirred for 1.5 hours at ambient temperature. Concentrated ammonium hydroxide (75 mL of 29%) and *p*-toluenesulfonyl chloride (1.7 g, 8.9 mmol) were then sequentially added with stirring, and the reaction was stirred for 45 minutes. The aqueous layer was separated and extracted with chloroform (1 x 50 mL). The combined organic fractions were washed with 5% aqueous sodium hydroxide solution (2 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The residue was recrystallized from a mixture of toluene (20 mL) and methanol (4 mL) and then recrystallized three times from 5:1 methanol:water (18 mL) and dried overnight in a vacuum oven at 80 °C. During the recrystallization, the product was mixed with material from another run to provide 0.720 g of 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylbutyramide as a tan solid, mp 177-179 °C.

Anal. Calcd for $C_{18}H_{23}N_5O{\cdot}0.19\ H_2O$: C, 65.75; H, 7.17; N, 21.30. Found: C, 65.91; H, 7.35; N, 21.32.

Example 4

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide



Part A

A solution of 4-(3-aminoquinolin-4-ylamino) ethyl butyrate (49.7 g, 182 mmol, prepared as described in Parts A and B of Example 3) in toluene (500 mL) was heated at reflux for 10 minutes and then cooled slightly. Trimethyl orthobutyrate (29.0 g, 197 mmol) and pyridinium *p*-toluenesulfonate (0.70 g, 2.8 mmol) were added, and the reaction was heated at reflux under a Dean-Stark trap for 1.5 hours while the distillate was periodically removed. The reaction was allowed to stand overnight at ambient temperature. The toluene was removed under reduced pressure; chloroform (500 mL) and

charcoal (4 g) were sequentially added. The resulting mixture was heated at reflux for one hour and then filtered through a layer of CELITE filter agent. The filtrate was washed with saturated aqueous sodium bicarbonate (100 mL), dried over potassium sulfate, filtered, and concentrated under reduced pressure to provide 49.4 g of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate as a dark oil.

Part B

Concentrated ammonium hydroxide (8.0 mL of 29%) was added to a solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate (5.1 g, 16 mmol) in 2-methyltetrahydrofuran (10 mL), and the mixture was heated overnight in a sealed high-pressure vessel at 80 °C. An analysis by liquid chromatography/mass spectrometry (LC/MS) indicated the reaction was incomplete. The solvents were evaporated under a stream of nitrogen, and ammonium acetate (10 g) was added. The vessel was sealed and heated overnight at 135 °C. The reaction was allowed to cool to ambient temperature, and water (50 mL) was added. The mixture was filtered, and the filtrate was washed with saturated aqueous sodium bicarbonate (25 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 2.95 g of 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide as a light brown solid.

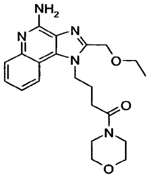
Part C

4-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide (2.90 g, 9.78 mmol) was treated with mCPBA (5.5 g, 25 mmol), concentrated ammonium hydroxide (100 mL of 29%), and *p*-toluenesulfonyl chloride (2.80 g, 14.7 mmol) according to the method described in Part E of Example 3. After the reaction solution was dried with potassium carbonate, it was decanted, and charcoal (2 g) was added. The mixture was heated at reflux for two hours, filtered through a layer of CELITE filter agent, and concentrated under reduced pressure. The crude solid was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol) and combined with material from another run. The solid was recrystallized from 5:1 toluene:methanol (18 mL), dried overnight in a vacuum oven, recrystallized from ethanol:water, and dried overnight in a vacuum oven to provide 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide as a tan solid, mp 249-251 °C.

Anal. Calcd for $C_{17}H_{21}N_5O$: C, 65.57; H, 6.80; N, 22.49. Found: C, 65.24; H, 6.79; N, 22.16.

Example 5

4-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one



Part A

A suspension of 4-chloro-3-nitroquinoline (40.0 g, 0.192 mol) in chloroform (250 mL) was cooled to 0 °C; triethylamine (75 mL, 0.54 mol) was added. Ethyl 4-aminobutyrate hydrochloride (35.0 g, 0.210 mol), prepared as described in Part A of Example 1, was added in portions over a period of two minutes. The reaction was stirred at 0 °C for 15 minutes, allowed to warm to ambient temperature, and stirred overnight. The reaction was heated at reflux for 15 minutes, and then chloroform (200 mL) was added. The resulting solution was washed with water (5 x 150 mL) and then used in Part B.

Part B

Water (400 mL), potassium carbonate (105 g, 0.760 mol), ethyl viologen dibromide (0.50 g, 1.3 mmol), and sodium hydrosulfite (115 g, 0.660 mol) were sequentially added to the solution from Part A. The reaction was stirred at ambient temperature for three days. The organic layer was separated and washed with water (3 x 200 mL), dried over potassium carbonate, and concentrated under reduced pressure to provide 48.4 g of 4-(3-aminoquinolin-4-ylamino) ethyl butyrate as an orange oil.

Part C

A solution of ethoxyacetyl chloride (6.61 g, 54.0 mmol) in dichloromethane (10 mL) was added dropwise to a solution of 4-(3-aminoquinolin-4-ylamino) ethyl butyrate (11.8 g, 43.2 mmol) in dichloromethane (150 mL). The reaction was stirred for 30 minutes and then concentrated under reduced pressure. Triethylamine (16.7 g, 165 mmol)

and ethanol (150 mL) were added, and the resulting solution was heated at reflux for four hours. The solvent was removed under reduced pressure. Dichloromethane (75 mL) was added, and the resulting solution was washed sequentially with water (3 x 75 mL) and saturated aqueous sodium bicarbonate (75 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 12.5 g of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl butyrate as a dark oil.

Part D

4-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl butyrate (6.25 g, 18.3 mmol) and morpholine (16.0 g, 184 mmol) were sealed and heated in a high-pressure vessel at 130 °C overnight. An analysis by TLC indicated the reaction was incomplete. Pyridinium *p*-toluenesulfonate (100 mg) was added, and the reaction was heated for three days at 105 °C and for one day at 125 °C. The solution was allowed to cool and then poured into water (100 mL). The resulting solution was extracted with dichloromethane (3 x 75 mL), and the combined extracts were dried over potassium carbonate, filtered, and concentrated under reduced pressure. The residue was mixed with ethyl acetate (50 mL) and hexane (200 mL) and sonicated. The solvent was decanted away to afford 6.9 g of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one as an oil.

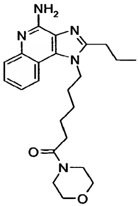
Part E

4-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one (6.9 g, 18 mmol) was treated with mCPBA (7.9 g, 35 mmol), concentrated ammonium hydroxide (50 mL of 29%), and *p*-toluenesulfonyl chloride (6.0 g, 32 mmol) according to a modification of the method described in Part E of Example 3. The mCPBA addition was carried out at 0 °C, and the reaction was carried out in dichloromethane (150 mL). The crude product was triturated with 2:1 ethyl acetate:hexane (15 mL), and the resulting solid was isolated by filtration, washed with 30:70 ethyl acetate:hexane, recrystallized twice from methanol:water, and dried overnight in a vacuum oven at 70 °C to provide 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one as yellow crystals, mp 201-203 °C.

Anal. Calcd for $C_{21}H_{27}N_5O_3$: C, 63.46; H, 6.85; N, 17.62. Found: C, 63.24; H, 6.84; N, 17.54.

Example 6

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one



Part A

Anhydrous ethanol (400 mL) was cooled to -78 °C, and thionyl chloride (63.34 mL, 868.4 mmol) was added. The reaction was stirred for one hour at -78 °C, and solid 6-aminocaproic acid (100.0 g, 723.7 mmol) was then added. The reaction was allowed to warm to ambient temperature slowly, stirred overnight, and then concentrated under reduced pressure. The residue was recrystallized from ethyl acetate:diethyl ether to provide 137 g of ethyl 6-aminocaproate hydrochloride as a white solid.

Part B

Potassium carbonate (6.62 g, 47.9 mmol) and triethylamine (16.7 mL, 0.120 mol) were sequentially added with stirring to a solution of 4-chloro-3-nitroquinoline (10.0 g, 47.9 mmol) in chloroform (200 mL). After 15 minutes, ethyl 6-aminocaproate hydrochloride (11.23 g, 57.52 mmol) was slowly added, and the reaction was stirred for two hours; washed sequentially with water (200 mL), saturated aqueous sodium bicarbonate, and brine; dried over magnesium sulfate; filtered; concentrated under reduced pressure; and used in Part C without purification.

Part C

The material from Part B was hydrogenated according to the method described in Part C of Example 1 to provide 15.0 g of 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate.

Part D

Trimethyl orthobutyrate (15.0 g, 49.8 mmol) and pyridinium *p*-toluenesulfonate (0.20 g, 0.80 mmol) were added to a solution 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate (15.0 g, 49.8 mmol) in toluene (400 mL), and the reaction was heated at reflux

under a Dean-Stark trap for 4.5 hours while the distillate was periodically removed. The reaction was allowed to cool to ambient temperature, washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate, which was used without purification.

Part E

A solution of sodium hydroxide (4.35 g, 109 mmol) in water (50 mL) was added to a solution of the material from Part D in ethanol (100 mL), and the reaction was stirred at ambient temperature for three hours. Additional sodium hydroxide (2.2 g, 55 mmol) was added, and the reaction was stirred for an additional hour and then concentrated under reduced pressure. The residue was diluted with water (100 mL) and adjusted to pH 5 with the addition of 10% hydrochloric acid. The mixture was extracted three times with chloroform, and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 12.4 g of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid.

Part F

A solution of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid (3.0 g, 9.2 mmol) in anhydrous dichloromethane (50 mL) was cooled to 0 °C. Oxalyl chloride (1.44 mL, 16.6 mmol) was added dropwise over a period of 15 minutes. The resulting solution was allowed to warm to ambient temperature and stirred for one hour and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), and morpholine (2.41 mL, 27.6 mmol) was added. The reaction was stirred overnight, washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 3.6 g of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one.

Part G

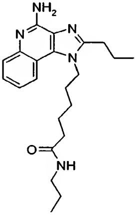
Under a nitrogen atmosphere, a solution of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one (3.6 g, 9.1 mmol) in chloroform (100 mL) was treated with mCPBA (6.29 g, 36.5 mmol). The reaction was stirred for two hours, washed sequentially with saturated aqueous sodium bicarbonate (3 x) and brine, dried over magnesium sulfate, and filtered. Concentrated ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.60 g, 13.7 mmol) were added sequentially to the filtrate. The

reaction was stirred vigorously for two hours, and then the organic layer was separated and washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) followed by recrystallization from ethyl acetate:hexane to provide 0.84 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one as brown needles, mp 149-151 °C.

Anal. Calcd for $C_{23}H_{31}N_5O_2$: C, 67.46; H, 7.63; N, 17.12. Found: C, 67.28; H, 7.56; N, 16.75.

Example 7

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide



Part A

6-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid (3.0 g, 9.2 mmol, prepared in Parts A through E of Example 6) was treated with oxalyl chloride (1.45 mL, 16.6 mmol) and *n*-propylamine (2.27 mL, 27.6 mmol) according to the method described in Part F of Example 6 to provide 3.4 g of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide. The acid chloride solution was cooled to 0 °C before the addition of *n*-propylamine.

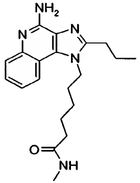
Part B

mCPBA (6.4 g, 37.1 mmol) was added to a solution of the material from Part A in chloroform (75 mL). The reaction was stirred for two hours, washed sequentially with saturated aqueous sodium bicarbonate (2 x) and brine, dried over magnesium sulfate, and

filtered. Concentrated ammonium hydroxide (40 mL) was added to the filtrate. The mixture was stirred for ten minutes before the addition of *p*-toluenesulfonyl chloride (2.65 g, 13.9 mmol). The reaction was stirred vigorously for two hours, and then the organic layer was separated and washed sequentially with 10% sodium hydroxide (2 x) and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 97:3 to 95:5) followed by recrystallization from methanol:water to provide 0.45 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide as brown needles, mp 139-141°C.
Anal. Calcd for $C_{22}H_{31}N_5O \cdot 0.44\ H_2O$: C, 67.85; H, 8.25; N, 17.98. Found: C, 67.80; H, 8.22; N, 17.82.

Example 8

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylhexanamide



Part A

A solution of sodium hydrosulfite (73.55 g, 422.4 mmol) and potassium carbonate (65.9 g, 476 mmol) in water (200 mL) was stirred for 15 minutes. A mixture of ethyl 6-(3-nitroquinolin-4-ylamino)hexanoate (40.0 g, 121 mmol, prepared as described in Parts A and B of Example 6), 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide (0.65 g, 1.2 mmol), dichloromethane (200 mL), and water (40 mL) was added over a period of five minutes, and the reaction was stirred overnight at ambient temperature. Water (100 mL) was added; the organic layer was separated and washed with water (3 x 150 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 25.15 g of 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate. The product was mixed with material from another run.

Part B

A solution of 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate (44.0 g, 146 mmol) in toluene (500 mL) was heated at reflux under a Dean-Stark trap for 1.5 hours and then allowed to cool to ambient temperature. Trimethyl orthobutyrate (29.2 mL, 182.5 mmol) and pyridinium *p*-toluenesulfonate (0.300 g, 1.20 mmol) were sequentially added, and the reaction was heated at reflux for three hours, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was dissolved in dichloromethane, and the resulting solution was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 97:3 dichloromethane:methanol) to provide 38 g of ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate.

Part C

The method described in Part D of Example 3 was used to treat ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (5.0 g, 14 mmol) with methylamine (8 mL of a 40% solution). The reaction was complete after being stirred overnight at 70 °C. Following the work-up procedure, 3.42 g of *N*-methyl-6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide were obtained.

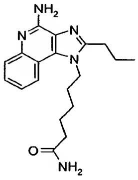
Part D

mCPBA (5.0 g, 29.03 mmol) was added to a solution of *N*-methyl-6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide (3.42 g, 9.67 mmol) in chloroform (100 mL). The reaction was stirred for two hours at ambient temperature and then washed with 10% aqueous sodium hydroxide. Ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.39 g, 12.6 mmol) were sequentially added, and the reaction was stirred vigorously for two hours. The organic layer was separated and washed sequentially with 10% sodium hydroxide, saturated aqueous sodium bicarbonate, and brine; dried over magnesium sulfate; filtered; and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) followed by recrystallization from methanol:water to provide 1.055 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylhexanamide as beige needles, mp 158-159 °C.

Anal. Calcd for $C_{20}H_{27}N_5O$: C, 67.96; H, 7.70; N, 19.81. Found: C, 67.65; H, 7.45; N, 19.74.

Example 9

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide



Part A

A solution 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate (25.15 g, 83.4 mmol, prepared in Part A of Example 8) in toluene (400 mL) was treated with trimethyl orthobutyrate (15.4 mL, 96.2 mmol) and pyridinium *p*-toluenesulfonate (0.20 g, 0.80 mmol) according to a modification of the method described in Part D of Example 6. The reaction was not complete after five hours and was allowed to cool to ambient temperature overnight. Additional pyridinium *p*-toluenesulfonate (0.20 g, 0.80 mmol) and trimethyl orthobutyrate (2.0 mL, 12 mmol) were added. The reaction was heated at reflux for two hours and then subjected to the work-up procedure to provide 25.0 g of ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate.

Part B

Ammonium acetate (20 g) and ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (4.11 g, 11.6 mmol) were heated overnight at 140 °C in a sealed vessel. The reaction was allowed to cool to ambient temperature, and saturated aqueous sodium bicarbonate was added. The mixture was extracted with chloroform (3 x), and the extracts were combined and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) to provide 1.7 g of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide.

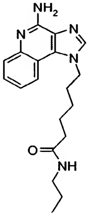
Part C

6-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide (1.7 g, 5.2 mmol) was treated with mCPBA (3.61 g, 15.7 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (1.49 g, 7.84 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part D of Example 8 to provide 0.137 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide as tan needles, mp 210-211°C.

Anal. Calcd for $C_{19}H_{25}N_5O$: C, 67.23; H, 7.42; N, 20.63. Found: C, 66.95; H, 7.76; N, 20.43.

Example 10

6-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide



Part A

Triethyl orthoformate (12.74 mL, 76.64 mmol) and pyridinium *p*-toluenesulfonate (0.200 g) were sequentially added to a solution of 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate (16.5 g, 54.7 mmol, prepared as described in Part A of Example 8) in toluene (200 mL), and the reaction was heated at reflux under a Dean-Stark trap for four hours, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was dissolved in dichloromethane, and the resulting solution was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 16.4 g of ethyl 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate.

Part B

A solution of ethyl 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (7.0 g, 22.5 mmol) and *n*-propylamine (11.1 mL, 135 mmol) in THF (10 mL) was heated at 100 °C for ten days in a sealed high-pressure vessel. Additional *n*-propylamine (20 mL) was added after three days and again after seven days. After ten days, the reaction was concentrated under reduced pressure to provide 7.0 g of 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide.

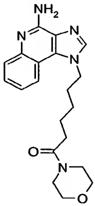
Part C

6-(1*H*-Imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide (7.0 g, 26 mmol) was treated with mCPBA (8.68 g, 37.7 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (8.01 g, 42.1 mmol) according to the method described in Part D of Example 8. The crude product was triturated with ethyl acetate and recrystallized twice from methanol:water to provide 2.00 g of 6-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide as brown needles, mp 128-130 °C.

Anal. Calcd for $C_{19}H_{25}N_5O{\bullet}0.20\ H_2O$: C, 66.52; H, 7.46; N, 20.42. Found: C, 66.12; H, 7.38; N, 20.10.

Example 11

6-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one



Part A

A solution of sodium hydroxide (1.66 g, 41.7 mmol) in water (15 mL) was added to a solution of ethyl 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (10.0 g, 32.1 mmol, prepared in Part A of Example 10) in ethanol (75 mL), and the reaction was stirred at ambient temperature for two hours and then concentrated under reduced pressure. The

residue was diluted with water and adjusted to pH 5 with the addition of 10% hydrochloric acid. The mixture was extracted with dichloromethane, and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 2.5 g of 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid.

Part B

6-(1*H*-Imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid (2.5 g, 8.8 mmol) was treated with oxalyl chloride (1.39 mL, 15.9 mmol) and morpholine (2.31 mL, 26.5 mmol) according to a modification of the method described in Part F of Example 6. The reaction with oxalyl chloride was carried out at ambient temperature, and the reaction with morpholine was complete after one hour. Following the work-up procedure, 3.1 g of 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one were obtained.

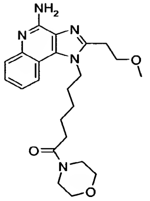
Part C

6-(1*H*-Imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one (3.09 g, 8.79 mmol) was treated with mCPBA (3.54 g, 15.4 mmol) followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (3.26 g, 17.4 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part C of Example 10 to provide 0.422 g of 6-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one as brown needles, mp 166-168 °C.

Anal. Calcd for $C_{20}H_{25}N_5O_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.09; H, 6.75; N, 18.87.

Example 12

6-[4-Amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylhexan-1-one



Part A

Methoxypropionyl chloride (4.85 g, 39.8 mmol) was added dropwise over a period of ten minutes to a solution of 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate (10.0 g, 33.2 mmol, prepared as described in Part A of Example 8) in dichloromethane (200 mL). The reaction was stirred for one hour at ambient temperature and then concentrated under reduced pressure. Triethylamine (18.49 g, 132.7 mmol) and ethanol (200 mL) were added, and the resulting solution was heated at reflux for three hours. The solvent was removed under reduced pressure. Dichloromethane (75 mL) was added, and the resulting solution was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 12.05 g of ethyl 6-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]hexanoate as a dark oil.

Part B

Ethyl 6-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]hexanoate (12.05 g, 32.61 mmol) was treated with sodium hydroxide (1.70 g, 42.4 mmol) according to a modification of the method described in Part A of Example 11. The reaction was stirred overnight at ambient temperature to provide 8.35 g of 6-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]hexanoic acid after the aqueous work-up procedure.

Part C

6-[2-(2-Methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]hexanoic acid (4.1 g, 12 mmol) was treated with oxalyl chloride (1.89 mL, 21.6 mmol) and morpholine (3.15 mL, 36.0 mmol) according to a modification of the method described in Part F of Example 6.

The reaction with oxalyl chloride was carried out at ambient temperature, and the reaction with morpholine was complete after two hours. Following the work-up procedure, 4.55 g of 6-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylhexan-1-one were obtained.

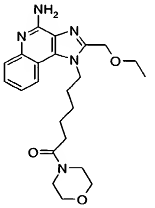
Part D

6-[2-(2-Methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylhexan-1-one (4.55 g, 11.1 mmol) was treated with mCPBA (4.97 g, 21.6 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (3.69 g, 19.4 mmol) according to the method described in Part D of Example 8. The crude product was recrystallized twice from ethyl acetate to provide 1.17 g of 6-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylhexan-1-one as brown needles, mp 131-132 °C.

Anal. Calcd for $C_{23}H_{31}N_5O_3 \cdot 0.14\ H_2O$: C, 64.54; H, 7.37; N, 16.36. Found: C, 64.14; H, 7.43; N, 16.40.

Example 13

6-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one



Part A

Ethyl 6-(3-nitroquinolin-4-ylamino)hexanoate (27.1 g, 81.8 mmol, prepared as described in Parts A and B of Example 6) was treated with sodium hydrosulfite (49.8 g, 286 mmol), potassium carbonate (44.6 g, 323 mmol), and ethyl viologen dibromide (0.306 g, 0.818 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional sodium hydrosulfite (5.0 g, 29

mmol) was added, and the reaction was stirred for one additional hour. The organic layer was separated, washed three times with water, and concentrated under reduced pressure to provide 24 g of 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate.

Part B

A solution of 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate (9.25 g, 30.7 mmol) in chloroform (100 mL) was cooled to 0 °C; triethylamine (5.13 mL, 36.8 mmol) was added. Ethoxyacetyl chloride (4.51 g, 36.8 mmol) was then added dropwise over a period of five minutes. The reaction was allowed to warm to ambient temperature, heated at reflux overnight, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 93:7 dichloromethane:methanol) to provide 7.73 g of 6-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl hexanoate.

Part C

A solution of 6-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl hexanoate (4.0 g, 11 mmol) in morpholine (7 mL) was heated at reflux for three days, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was dissolved in dichloromethane; the resulting solution was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 4.4 g of 6-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one.

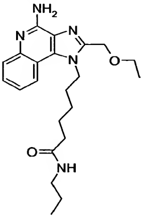
Part D

6-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one (4.4 g, 11 mmol) was treated with mCPBA (5.54 g, 32.1 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.74 g, 14.4 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part D of Example 8 and then dried for two days at 60 °C to provide 1.061 g of 6-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one as a beige powder, mp 160-162 °C.

Anal. Calcd for $C_{23}H_{31}N_5O_3 \cdot 0.47\ H_2O$: C, 63.65; H, 7.42; N, 16.14. Found: C, 63.64; H, 7.42; N, 16.05.

Example 14

6-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide



Part A

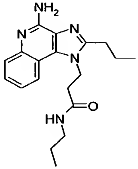
A solution of 6-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl hexanoate (3.73 g, 10.1 mmol, prepared in Parts A and B of Example 13), *n*-propylamine (5 mL), and THF (5 mL) was heated at 80 °C for three days in a high-pressure vessel, allowed to cool to ambient temperature, and concentrated under reduced pressure. The work-up procedure described in Part C of Example 13 was followed to provide 4.1 g of 6-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide.

Part B

6-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide (4.1 g, 11 mmol) was treated with mCPBA (5.74 g, 33.3 mmol) followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (2.85 g, 14.9 mmol) according to the method described in Part D of Example 8. The crude product was purified by column chromatography on silica gel (eluting with 97:3 dichloromethane:methanol) followed by recrystallization from methanol:water to provide 0.548 g of 6-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylhexanamide as beige needles, mp 161-162 °C. Anal. Calcd for $C_{22}H_{31}N_5O_2$: C, 66.47; H, 7.86; N, 17.62. Found: C, 66.27; H, 7.94; N, 17.38.

Example 15

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide



Part A

Potassium carbonate (19.87 g, 143.8 mmol) and triethylamine (50.1 mL, 359 mmol) were sequentially added with stirring to a solution of 4-chloro-3-nitroquinoline (30.0 g, 144 mmol) in chloroform (200 mL). After 15 minutes, β-alanine ethyl ester hydrochloride (26.5 g, 173 mmol) was slowly added, and the reaction was stirred overnight at ambient temperature. Water (100 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 27.4 g of ethyl 3-(3-nitroquinolin-4-ylamino)propionate as a yellow solid, which was used without purification.

Part B

Ethyl 3-(3-nitroquinolin-4-ylamino)propionate (28.2 g, 97.5 mmol) was treated with sodium hydrosulfite (50.9 g, 292 mmol), potassium carbonate (53.2 g, 385 mmol), and ethyl viologen dibromide (0.364 g, 0.973 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional sodium hydrosulfite (5.0 g, 29 mmol) was added, and the reaction was stirred for two additional hours. Additional sodium hydrosulfite (2.0 g, 5.3 mmol) was added, and the reaction was stirred for one additional hour. An analysis by TLC indicated the reaction was complete. The organic layer was separated, washed three times with water, and concentrated under reduced pressure to provide 20.7 g of 3-(3-aminoquinolin-4-ylamino) ethyl propionate.

Part C

3-(3-Aminoquinolin-4-ylamino) ethyl propionate (10.0 g, 38.6 mmol) was treated according to a modification of the method described in Part B of Example 8. After the addition of trimethyl orthobutyrate (7.71 mL, 48.2 mmol) and pyridinium *p*-toluenesulfonate (0.200 g, 0.796 mmol), the reaction was heated at reflux for one hour and subjected to the work-up procedure to provide 12.3 g of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate, which was used without purification.

Part D

A solution of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (3.45 g, 11.1 mmol), *n*-propylamine (9.1 mL, 110 mmol), and THF (5 mL) was heated at 80 °C for two days in a high-pressure vessel, allowed to cool to ambient temperature, and concentrated under reduced pressure to provide 3.5 g of 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide.

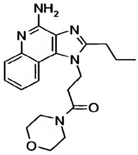
Part E

3-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide (3.5 g, 11 mmol) was treated with mCPBA (5.85 g, 32.4 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.76 g, 14.6 mmol) according to a modification of the method described in Part D of Example 8. When the reaction was complete, the organic layer was separated, washed with 10% aqueous sodium bicarbonate, and concentrated under reduced pressure. The crude product was purified as described in Part D of Example 8 to provide 1.026 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide as beige needles, mp 157-158 °C.

Anal. Calcd for $C_{19}H_{25}N_5O \cdot 0.97\ H_2O$: C, 63.94; H, 7.61; N, 19.62. Found: C, 63.95; H, 7.69; N, 19.55.

Example 16

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one



Part A

Ethyl 3-(3-nitroquinolin-4-ylamino)propionate (41.6 g, 144 mmol, prepared as described in Part A of Example 15) was treated with sodium hydrosulfite (87.62 g, 503.3 mmol), potassium carbonate (78.5 g, 568 mmol), and ethyl viologen dibromide (0.54 g, 1.4 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional sodium hydrosulfite (5.0 g, 29 mmol) was added, and the reaction was stirred for one additional hour. The organic layer was separated, washed with water (5 x 200 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 33.3 g of 3-(3-aminoquinolin-4-ylamino) ethyl propionate.

Part B

3-(3-Aminoquinolin-4-ylamino) ethyl propionate (33.3 g, 128 mmol) was treated according to a modification of the method described in Part B of Example 8. After the addition of trimethyl orthobutyrate (25.6 mL, 161 mmol) and pyridinium *p*-toluenesulfonate (0.200 g, 0.796 mmol), the reaction was heated at reflux for two hours and subjected to the work-up procedure to provide 37.1 g of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate, which was used without purification.

Part C

A solution of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (4.0 g, 15 mmol) in morpholine (20 mL, 0.2 mol) was heated at reflux for two days, allowed to cool to ambient temperature, and concentrated under reduced pressure to provide 5.2 g of 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one.

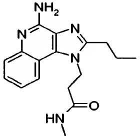
Part D

3-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one (5.2 g, 15 mmol) was treated with mCPBA (7.64 g, 44.3 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (3.79 g, 19.9 mmol) according to the method described in Part D of Example 8. The crude product was purified by column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol) followed by recrystallization from methanol:dichloromethane to provide 0.358 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one as yellow needles, mp 172-173 °C.

Anal. Calcd for $C_{20}H_{25}N_5O_2$•0.2 CH_3OH•0.2 H_2O: C, 64.27; H, 6.99; N, 18.55. Found: C, 64.20; H, 6.92; N, 18.67.

Example 17

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropionamide



Part A

A mixture of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (4.24 g, 16.5 mmol, prepared in Parts A and B of Example 16), THF (15 mL), and methylamine (available as a 40% solution in water, 8 mL) was sealed in a high-pressure vessel, heated at 80 °C overnight, and concentrated under reduced pressure to provide 4.7 g of *N*-methyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide.

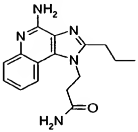
Part B

N-methyl-3-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide (4.7 g, 13 mmol) was treated with mCPBA (6.58 g, 38.2 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (3.27 g, 17.2 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part D of Example 8 to provide 0.674 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropionamide as a tan powder, mp 177-178 °C.

Anal. Calcd for $C_{17}H_{21}N_5O{\bullet}0.22\ H_2O$:C, 64.75; H, 6.85; N, 22.21. Found: C, 65.01; H, 6.97; N, 22.20.

Example 18

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide hydrochloride



Part A

Ethyl 3-(3-nitroquinolin-4-ylamino)propionate (62.0 g, 214 mmol, prepared as described in Part A of Example 15) was treated with sodium hydrosulfite (130.6 g, 750.1 mmol), potassium carbonate (117 g, 847 mmol), and ethyl viologen dibromide (0.802 g, 2.14 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional water (100 mL), dichloromethane, and sodium hydrosulfite (20.0 g, 115 mmol) were added, and the reaction was stirred for three additional hours. The organic layer was separated; washed with water (6 x), saturated aqueous sodium bicarbonate, and brine; dried over magnesium sulfate; filtered; and concentrated under reduced pressure to provide 40.2 g of 3-(3-aminoquinolin-4-ylamino) ethyl propionate.

Part B

3-(3-Aminoquinolin-4-ylamino) ethyl propionate (11.0 g, 42.4 mmol) was treated according to a modification of the method described in Part B of Example 8. After the addition of trimethyl orthobutyrate (7.8 mL, 49 mmol) and pyridinium *p*-toluenesulfonate (0.200 g, 0.796 mmol), the reaction was heated at reflux for one hour and subjected to the work-up procedure to provide 10.6 g of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate, which was used without purification.

Part C

Ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (5.0 g, 16 mmol) was treated with ammonium acetate (25.0 g) according to the method described in Part B

of Example 9 to provide 3.9 g of 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide, which was used without purification.

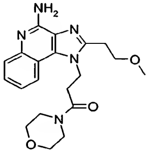
Part D

3-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide (3.9 g, 14 mmol) was treated with mCPBA (6.19 g, 26.9 mmol) followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (4.6 g, 24 mmol) according to the method described in Part D of Example 8. The crude product was dissolved in methanol, and hydrogen chloride (1.25 mL of a 1 M solution in diethyl ether) was added. The resulting solid was isolated by filtration and dried overnight under high vacuum to provide 0.477 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide hydrochloride as tan needles, mp 242-243 °C.

Anal. Calcd for $C_{16}H_{19}N_5O$•1.0 HCl•0.04 H_2O: C, 54.82; H, 6.29; N, 19.98. Found: C, 54.81; H, 6.66; N, 19.81.

Example 19

3-[4-Amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylpropan-1-one



Part A

The method described in Part A of Example 12 was used to treat 3-(3-aminoquinolin-4-ylamino) ethyl propionate (9.82 g, 37.9 mmol, prepared in Part A of Example 18) with methoxypropionyl chloride (5.54 g, 45.4 mmol). The reaction with triethylamine (21.1 mL, 151 mmol) was heated at reflux for six hours and then subjected to the work-up procedure to provide 10.3 g of ethyl 3-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propionate.

Part B

A solution of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (4.0 g, 15 mmol), morpholine (13.49 mL, 154.3 mmol), and 2-methyltetrahydrofuran (10 mL) was heated for three days in a high-pressure vessel at 120 °C, allowed to cool to ambient temperature, and concentrated under reduced pressure to provide 5.6 g of 3-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylpropan-1-one.

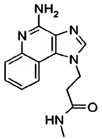
Part C

3-[2-(2-Methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylpropan-1-one (4.7 g, 13 mmol) was treated with mCPBA (5.73 g, 24.9 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (4.23 g, 22.2 mmol) according to the method described in Part D of Example 8. The crude product was recrystallized twice from ethyl acetate to provide 0.233 g of 3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylpropan-1-one as beige needles, mp 125-126 °C.

Anal. Calcd for $C_{20}H_{25}N_5O_3 \cdot 0.29\ H_2O$: C, 61.81; H, 6.63; N, 18.02. Found: C, 61.57; H, 6.45; N, 17.76.

Example 20

3-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropionamide



Part A

The method described in Part A of Example 10 was used to treat 3-(3-aminoquinolin-4-ylamino) ethyl propionate (10.0 g, 38.6 mmol, prepared in Part A of Example 18) with triethyl orthoformate (8.98 mL, 54.0 mmol). The reaction was complete in three hours. The reaction mixture was filtered to remove a precipitate and then subjected to the work-up procedure to provide 9.7 g of ethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate.

Part B

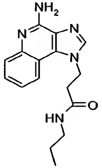
A mixture of ethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (4.70 g, 17.5 mmol), THF (5 mL), and methylamine (available as a 40% solution in water, 10 mL) was sealed in a high-pressure vessel, stirred at 100 °C overnight, and concentrated under reduced pressure to provide 4.4 g of 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropionamide.

Part C

mCPBA (8.95 g, 38.9 mmol) was added to a solution of 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropionamide (4.4 g, 15.6 mmol) in chloroform (100 mL); the reaction was stirred for one hour at ambient temperature. Ammonium hydroxide (40 mL) was added, and the mixture was stirred vigorously for 15 minutes. *p*-Toluenesulfonyl chloride (5.94 g, 31.2 mmol) was added over a period of ten minutes, and the reaction was stirred for two hours. The reaction mixture was filtered to remove a precipitate, and the organic layer was separated and washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystallized from methanol to provide 0.535 g of 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methylpropionamide as off-white needles, mp > 260 °C. Anal. Calcd for $C_{14}H_{15}N_5O{\bullet}0.13\ H_2O$: C, 61.90; H, 5.66; N, 25.78. Found: C, 61.51; H, 5.39; N, 25.41.

Example 21

3-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide



Part A

Ethyl 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (3.75 g, 13.9 mmol, prepared as described in Part A of Example 20) was treated with *n*-propylamine (11.4 mL, 139

mmol) according to the method described in Part B of Example 20 to provide 3.9 g of 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide.

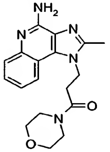
Part B

mCPBA (5.6 g, 24 mmol) was added to a solution of 3-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide (3.9 g, 14 mmol) in chloroform (100 mL). The reaction was stirred for two hours and washed with saturated aqueous sodium bicarbonate. Concentrated ammonium hydroxide (40 mL) was added. The mixture was stirred vigorously for five minutes before the addition of *p*-toluenesulfonyl chloride (5.13 g, 26.9 mmol). The reaction was stirred vigorously for two hours, and then the organic layer was separated and washed sequentially with saturated aqueous sodium bicarbonate (2 x) and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystallized three times from ethyl acetate to provide 0.496 g of 3-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide as a brown powder, mp 212-214 °C.

Anal. Calcd for $C_{16}H_{19}N_5O{\bullet}0.04\ H_2O$: C, 64.47; H, 6.45; N, 23.49. Found: C, 64.09; H, 6.64; N, 23.52.

Example 22

3-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one



Part A

4-Chloro-3-nitroquinoline (76.1 g, 365 mmol) was treated with β-alanine ethyl ester hydrochloride (50.0 g, 326 mmol) in the presence of triethylamine (94.5 mL, 678 mmol) and potassium carbonate (37.45 g, 271.2 mmol) according to a modification of the method described in Part A of Example 15. Before the addition of β-alanine ethyl ester hydrochloride, the reaction was cooled to 0 °C. After this addition, the reaction was

stirred for four hours at ambient temperature and subjected to the work-up procedure to provide 105 g of ethyl 3-(3-nitroquinolin-4-ylamino)propionate.

Part B

Ethyl 3-(3-nitroquinolin-4-ylamino)propionate (50.0 g, 173 mmol) was hydrogenated in the presence of 5% platinum on carbon (1.0 g) according to the method described in Part C of Example 1. The reaction was allowed to proceed overnight under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) and then subjected to the work-up procedure to provide 42.3 g of 3-(3-aminoquinolin-4-ylamino) ethyl propionate.

Part C

3-(3-Aminoquinolin-4-ylamino) ethyl propionate (15.0 g, 57.8 mmol) was treated with trimethyl orthoacetate (10.3 mL, 81.0 mmol) and pyridinium *p*-toluenesulfonate (0.200 g) according to the method described in Part A of Example 10 to provide 14.0 g of ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate as a brown solid.

Part D

A solution of ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (4.0 g, 15 mmol) and morpholine (10 mL, 100 mmol) was heated for three days in a high-pressure vessel at 100 °C, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was dissolved in dichloromethane, and the resulting solution was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 4.8 g of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one.

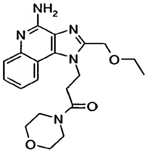
Part E

3-(2-Methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one (4.8 g, 15 mmol) was treated with mCPBA (5.95 g, 25.9 mmol) followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (5.49 g, 28.8 mmol) according to a modification of the method described in Part D of Example 8. The reaction was not washed with 10% aqueous sodium hydroxide prior to the addition of ammonium hydroxide. After the amination reaction was stirred for two hours, water was added. Following the work-up procedure, the chromatographic purification was carried out eluting with 90:10 dichloromethane:methanol. The resulting product was triturated with ethyl acetate and isolated by filtration to provide 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one as brown needles, mp 166-169 °C.

Anal. Calcd for $C_{18}H_{21}N_5O_2$•0.50 H_2O: C, 62.05; H, 6.36; N, 20.10. Found: C, 61.67; H, 6.63; N, 19.93.

Example 23

3-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one



Part A

3-(3-Aminoquinolin-4-ylamino) ethyl propionate (20.0 g, 77.3 mmol, prepared in Parts A and B of Example 22) was treated with ethoxyacetyl chloride (11.29 g, 92.5 mmol) according to a modification the method described in Part A of Example 12. The reaction in dichloromethane (300 mL) was stirred for 1.5 hours, and after the addition of triethylamine (43.08 mL, 309.1 mmol) and ethanol (300 mL), the reaction was heated at reflux for four hours and then subjected to the work-up procedure to provide 25.0 g of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl propionate.

Part B

A solution of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl propionate (5.0 g, 15 mmol) and morpholine (10 mL, 100 mmol) was heated overnight in a high-pressure vessel at 90 °C. An analysis by HPLC indicated the reaction was incomplete. The reaction was then heated overnight in a high-pressure vessel at 110 °C, allowed to cool to ambient temperature, and concentrated under reduced pressure to provide 5.1 g of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one.

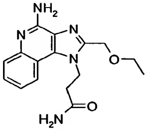
Part C

3-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one (5.1 g, 14 mmol) was treated with mCPBA (5.57 g, 24.2 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (5.14 g, 26.9 mmol) according to a modification of the method described in Part D of Example 8. The reaction

was not washed with 10% aqueous sodium hydroxide prior to the addition of ammonium hydroxide. The crude product was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol) and then triturated with ethyl acetate and isolated by filtration to provide 0.843 g of 3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpropan-1-one as off-white needles, mp 187-189 °C. Anal. Calcd for $C_{20}H_{25}N_5O_3$: C, 62.65; H, 6.57; N, 18.26. Found: C, 62.28; H, 6.83; N, 18.19.

Example 24

3-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide



Part A

Ammonium acetate (7 g) and 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl propionate (5.0 g, 15 mmol, prepared in Part A of Example 23) were stirred overnight at 125 °C in a sealed vessel. The reaction was allowed to cool to ambient temperature, and water (20 mL) was added. A precipitate formed and was isolated by filtration, washed with saturated aqueous sodium bicarbonate, and dried to provide 2.4 g of 3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide as a tan powder.

Part B

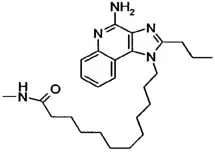
3-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide (2.4 g, 8.1 mmol) was treated with mCPBA (3.24 g, 14.1 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.99 g, 15.7 mmol) according to a modification of the method described in Part D of Example 8. The reaction was not washed with 10% aqueous sodium hydroxide prior to the addition of ammonium hydroxide. After the amination reaction was stirred for two hours, 10% aqueous sodium hydroxide (25 mL) and saturated aqueous sodium bicarbonate (25 mL) were sequentially added with stirring. A precipitate formed and was isolated by filtration. The solid was triturated twice with 25% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried in a

vacuum oven for three days to provide 0.685 g of 3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide as tan needles, mp >250 °C.

Anal. Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.03; H, 6.11; N, 22.24.

Example 25

12-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methyldodecanamide



Part A

Ethanol (150 mL) was cooled to 0 °C, and thionyl chloride (16.57 mL, 139.3 mmol) was added over a period of ten minutes. The reaction was stirred for ten minutes at 0 °C, and 12-aminododecanoic acid (25.0 g, 116 mol) was then added. The reaction was allowed to warm to ambient temperature, stirred at a slightly elevated temperature for one hour, and stirred at ambient temperature for two hours. The ethanol was removed under reduced pressure, and the solid residue was recrystallized from ethyl acetate. The crystals were isolated by filtration, washed with diethyl ether, and dried under vacuum to provide 37.4 g of ethyl 12-aminododecanoate hydrochloride as a white solid.

Part B

4-Chloro-3-nitroquinoline (15.52 g, 74.40 mmol) was treated with ethyl 12-aminododecanoate hydrochloride (25.0 g, 89.3 mmol) in the presence of potassium carbonate (10.28 g, 74.38 mmol) and triethylamine (25.9 mL, 186 mmol) according to a modification of the method described in Part A of Example 15. After the reaction was stirred for six hours, an analysis by TLC indicated the presence of starting material, and additional ethyl 12-aminododecanate hydrochloride (1.0 g, 3.6 mmol) was added. The reaction was stirred overnight and subjected to the work-up procedure to provide 31.0 g of 12-(3-nitroquinolin-4-ylamino) ethyl dodecanoate.

Part C

Water (25 mL) and ethyl viologen dibromide (0.279 g, 0.746 mmol) were added to a solution of the material from Part B. Sodium hydrosulfite (45.4 g, 261 mmol) and a solution of potassium carbonate (40.7 g, 295 mmol) in water (200 mL) were added, and the reaction was stirred overnight. An analysis by TLC indicated that the reaction was incomplete. Additional sodium hydrosulfite (5.0 g, 29 mmol) was added, and the reaction was stirred for 0.5 additional hour. The organic layer was separated, washed three times with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 12-(3-aminoquinolin-4-ylamino)dodecanoate.

Part D

Ethyl 12-(3-aminoquinolin-4-ylamino)dodecanoate (20.0 g, 51.8 mmol) was treated according to a modification of the method described in Part B of Example 8. Prior to the addition of trimethyl orthobutyrate (9.53 mL, 59.6 mmol) and pyridinium *p*-toluenesulfonate (0.500 g, 1.99 mmol), the reaction was heated at reflux for ten minutes. After the reaction was heated at reflux, it was allowed to cool to ambient temperature, washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure to provide 22.3 g of ethyl 12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanoate, which was used without purification.

Part E

A mixture of ethyl 12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanoate (4.0 g, 9.1 mmol), THF (5 mL), and methylamine (available as a 40% solution in water, 8 mL) was sealed in a high-pressure vessel and heated at 80 °C overnight. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane. The resulting solution was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 3.8 g of *N*-methyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide.

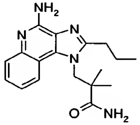
Part F

N-Methyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide (3.8 g, 9.0 mmol) was treated with mCPBA (4.65 g, 26.9 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (2.31 g, 12.1 mmol) according to the method described in Part D of Example 8. The crude product was purified as described in Part D

of Example 8 to provide 1.036 g of 12-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methyldodecanamide as a brown crystalline solid, mp 135-137 °C.
Anal. Calcd for $C_{26}H_{39}N_5O$: C, 71.36; H, 8.98; N, 16.0. Found: C, 71.12; H, 9.18; N, 15.90.

Example 26

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropionamide



Part A

Concentrated ammonium hydroxide (150 mL of 29%) was cooled to 0 °C in a high-pressure vessel; bromopivalic acid (30.0 g, 359 mmol) was added with stirring over a period of ten minutes. The reaction was stirred for 30 minutes, sealed, heated at 55 °C for three days, and allowed to cool to ambient temperature. The solution was concentrated under reduced pressure, and the residue was dissolved in ethanol (150 mL). The resulting solution was concentrated under reduced pressure; the residue was dissolved in toluene, which was removed under reduced pressure to provide a white solid.

Part B

The material from Part B was suspended in ethanol (300 mL) and cooled to 0 °C. Thionyl chloride (45.0 mL, 617 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature, stirred overnight, heated at reflux for one hour, and allowed to cool to ambient temperature. The volatiles were removed under reduced pressure, and the residue was mixed with ethyl acetate. The resulting mixture was filtered, and the filtrate was concentrated under reduced pressure to provide ethyl 3-amino-2,2-dimethylpropionate as a yellow oil, which was used without purification.

Part C

A suspension of 4-chloro-3-nitroquinoline (35.0 g, 168 mmol) and triethylamine (84 mL, 0.60 mol) in dichloromethane (400 mL) was cooled to 0 °C; a solution of ethyl 3-amino-2,2-dimethylpropionate (40.0 g, 0.220 mol) in dichloromethane (50 mL) was added

dropwise. The reaction was stirred at 0 °C for 30 minutes and then at ambient temperature for four hours. The reaction was incomplete as determined by a TLC analysis, and additional ethyl 3-amino-2,2-dimethylpropionate (10.0 g, 55.0 mmol) was added. The reaction was stirred overnight; another analysis by TLC indicated the reaction was incomplete. Additional ethyl 3-amino-2,2-dimethylpropionate (5.0 g, 28 mmol) was added, and the reaction was heated at reflux for three hours. Potassium carbonate (10 g) was added, and the reaction was heated at reflux for two hours and stirred overnight at ambient temperature. Saturated aqueous sodium bicarbonate (50 mL) was added, and the reaction was stirred for three days. The organic layer was separated, washed with water (3 x 100 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide ethyl 2,2-dimethyl-3-(3-nitroquinolin-4-ylamino)propionate as an orange oil, which was mixed with material from another run and used without purification.

Part D

A mixture of ethyl 2,2-dimethyl-3-(3-nitroquinolin-4-ylamino)propionate (59 g), sodium hydrosulfite (109 g, 532 mmol), potassium carbonate (103 g, 744 mmol), and ethyl viologen dibromide (0.50 g, 1.3 mmol), dichloromethane (350 mL), and water (350 mL) was stirred overnight at ambient temperature. The aqueous layer was separated and extracted with dichloromethane (100 mL). The combined organic fractions were washed with water (4 x 75 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 46.1 g of ethyl 3-(3-aminoquinolin-4-ylamino)-2,2-dimethylpropionate as a dark oil.

Part E

Ethyl 3-(3-aminoquinolin-4-ylamino)-2,2-dimethylpropionate (8.2 g, 29 mmol) was treated according to a modification of the method described in Part B of Example 8. Prior to the addition of trimethyl orthobutyrate (5.3 g, 36 mmol) and pyridinium *p*-toluenesulfonate (0.10 g, 0.40 mmol), the reaction was heated at reflux for ten minutes. During the work-up procedure, the solution was dried over potassium carbonate. The crude product was purified by column chromatography on silica gel (eluting with 93:7 dichloromethane:methanol containing 3 mL concentrated ammonium hydroxide per liter of eluent) to provide 2.1 g of ethyl 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate as an orange oil.

Part F

Aqueous sodium hydroxide (1 mL of 50%) was added to a mixture of ethyl 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (2.1 g, 6.2 mmol), ethanol (50 mL), and water (5 mL). The reaction was stirred for one hour at ambient temperature and concentrated under reduced pressure. The residue was extracted with dichloromethane (2 x 50 mL); the combined extracts were diluted with dichloromethane (100 mL). The resulting solution was treated with water (10 mL) and adjusted to pH 6 with the addition of concentrated hydrochloric acid (<1 mL). The aqueous layer was separated and extracted with dichloromethane (25 mL). The combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 0.45 g of 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionic acid hydrochloride as a yellow oil. The acidic aqueous layer was concentrated under reduced pressure and dried for one hour under vacuum at 55 °C to provide 1.5 g of 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionic acid hydrochloride as a yellow solid.

Part G

A suspension of the oil and the solid from Part F in dichloromethane (100 mL) was cooled to 0 °C, and a solution of oxalyl chloride (1.1 mL, 11 mmol) in dichloromethane (4 mL) was added. After the addition, the reaction was stirred for 30 minutes at ambient temperature and concentrated under reduced pressure. A second treatment with oxalyl chloride was carried out as described above. The residue was suspended in dichloromethane (75 mL) and cooled to 0 °C. A solution of ammonia (10 mL of 2 M in isopropanol) was then added over a period of two minutes. The reaction was stirred for 30 minutes and then concentrated under reduced pressure. The residue was mixed with dichloromethane (100 mL) and saturated aqueous sodium bicarbonate (25 mL). The aqueous layer was separated and extracted with dichloromethane (50 mL). The combined organic fractions were dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 1.0 g of 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropionamide as a yellow solid, which was combined with material from another run.

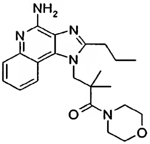
Part H

3-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropionamide was treated with mCPBA (3.24 g, 14.4 mmol) followed by ammonium hydroxide (75 mL)and *p*-toluenesulfonyl chloride (2.5 g, 13 mmol) according to a modification of the method

described in Part F of Example 1. The reaction was cooled to 0 °C before the addition of mCPBA. After the addition, the reaction was stirred for 15 minutes at 0 °C and 1.75 hours at ambient temperature. The reaction was not washed prior to the addition of ammonium hydroxide. The amination reaction was stirred for one hour. The crude product was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol), recrystallized from toluene:methanol, dried overnight in a vacuum oven at 80 °C, recrystallized from acetonitrile:water, and dried overnight in a vacuum oven at 80 °C to provide 0.553 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropionamide as a yellow solid, mp 219-221 °C.
Anal. Calcd for $C_{18}H_{23}N_5O$: C, 66.44; H, 7.12; N, 21.52. Found: C, 66.14; H, 7.04; N, 21.41.

Example 27

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethyl-1-morpholin-4-ylpropan-1-one



Part A

Ethyl 3-(3-aminoquinolin-4-ylamino)-2,2-dimethylpropionate (7.1 g, 25 mmol) was prepared according to the methods described in Parts A through D of Example 26 and treated according to a modification of the method described in Part B of Example 8. Prior to the addition of trimethyl orthobutyrate (4.0 g, 27 mmol) and pyridinium *p*-toluenesulfonate (0.10 g, 0.40 mmol), the reaction was heated at reflux for ten minutes. After the addition, the reaction was heated at reflux for four hours and allowed to stand at ambient temperature overnight. An analysis by TLC indicated the reaction was incomplete, and it was heated at reflux for an additional eight hours and allowed to stand for three days at ambient temperature. Additional pyridinium *p*-toluenesulfonate (0.10 g, 0.40 mmol) was added, and the reaction was heated at reflux for eleven hours and then

allowed to cool to ambient temperature. Ethyl acetate (100 mL) was added, and the resulting solution was washed with saturated aqueous sodium bicarbonate (3 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to 8 g of ethyl 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate as a dark oil, which was used without purification.

Part B

A solution of ethyl 2,2-dimethyl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (5.1 g, 15 mmol) and morpholine (5 mL, 60 mmol) was heated at reflux overnight. An analysis by LC/MS indicated the reaction was incomplete. The solution was then heated overnight in a high-pressure vessel at 165 °C. Again, an analysis by LC/MS indicated the reaction was incomplete. The volatiles were removed under reduced pressure, and the residue was dissolved in ethanol (30 mL). Aqueous sodium hydroxide (1.35 mL of 50%, 20.0 mmol) was added, and the reaction was stirred for 1.5 hours. The solution was adjusted to pH 7 with the addition of concentrated hydrochloric acid (~ 1 mL) and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (75 mL); a solution of oxalyl chloride (2.5 mL, 28 mmol) in dichloromethane (5 mL) was added dropwise over a period of two minutes. The reaction was stirred for 30 minutes, and additional oxalyl chloride (0.5 mL, 6 mmol) was added. The reaction was stirred for 30 minutes and diluted with dichloromethane (75 mL). A solution of morpholine (4.0 mL, 41 mmol) in dichloromethane (10 mL) was then added dropwise, and the reaction was stirred for two hours. The reaction was diluted with dichloromethane (45 mL), washed with saturated aqueous sodium bicarbonate (3 x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluting with 93:7 dichloromethane:methanol) to provide 5.8 g of 2,2-dimethyl-1-morpholin-4-yl-3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-propan-1-one as a semi-solid.

Part C

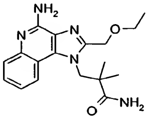
mCPBA (8.7 g, 39 mmol) was added to a solution of the material from Part B in chloroform (150 mL). The reaction was stirred for 1.75 hours at ambient temperature and then washed with 5% aqueous sodium hydroxide (2 x 50 mL). Ammonium hydroxide (150 mL) and *p*-toluenesulfonyl chloride (4.4 g, 23 mmol) were sequentially added, and the reaction was stirred vigorously for two hours. The aqueous layer was separated and

extracted with dichloromethane (50 mL). The combined organic fractions were washed with 5% sodium hydroxide (2 x 50 mL), dried over potassium carbonate, decanted, and concentrated under reduced pressure. The crude product was recrystallized several times from methanol:water to provide 1.84 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethyl-1-morpholin-4-ylpropan-1-one as a yellow solid, mp 212-214 °C.

Anal. Calcd for $C_{22}H_{29}N_5O_2 \cdot 0.15\ H_2O$: C, 66.35; H, 7.42; N, 17.59. Found: C, 66.15; H, 7.25; N, 17.82.

Example 28

3-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropionamide



Part A

A modification of the method described in Part C of Example 5 was used to treat ethyl 3-(3-aminoquinolin-4-ylamino)-2,2-dimethylpropionate (15.5 g, 60.2 mmol, prepared in Parts A through D of Example 26) with ethoxyacetyl chloride (8.7 g, 71 mmol) followed by triethylamine (24.4 mL, 175 mmol). The reaction with ethoxyacetyl chloride was stirred overnight, and the reaction with triethylamine was heated at reflux in ethanol (125 mL) for four days. Following the work-up procedure, the crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 100:0 to 95:5) to provide 7.9 g of ethyl 2,2-dimethyl-3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate as an oil.

Part B

Aqueous sodium hydroxide (1.5 mL of 50%, 19 mmol) was added to a mixture of ethyl 2,2-dimethyl-3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (5.0 g, 14 mmol), ethanol (50 mL), and water (5 mL). The reaction was stirred for two hours at ambient temperature; an analysis by TLC indicated that starting material was present. Additional aqueous sodium hydroxide (0.5 mL of 50%) was added, and the reaction was

heated at reflux for two hours and concentrated under reduced pressure. Ethanol (100 mL) was added to the residue and then removed under reduced pressure to provide 2,2-dimethyl-3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionic acid, which was dried overnight under vacuum.

Part C

A modification of the method described in Part G of Example 26 was used to treat the material from Part B with oxalyl chloride (2 x 2.6 mL, 59.6 mmol) followed by ammonia (5 mL of a 7 M solution in methanol). The reactions were carried out at ambient temperature, and the reaction with ammonia was stirred for two hours. Aqueous sodium hydroxide (5 mL of 50%) and water (45 mL) were added, and the mixture was stirred. The organic layer was separated, although not completely, and stirred with aqueous sodium hydroxide (10 mL of 25%). The organic fraction was separated and concentrated under reduced pressure to provide 2,2-dimethyl-3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide as a light-brown solid.

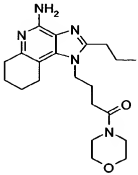
Part D

The material from Part C was treated with mCPBA (5.4 g, 24 mmol) followed by ammonium hydroxide (75 mL)and *p*-toluenesulfonyl chloride (4.1 g, 22 mmol) according to a modification of the method described in Part F of Example 1. The reaction was cooled to 0 °C before the addition of mCPBA. After the addition, the reaction was allowed to warm to ambient temperature and stirred for 2.25 hours. Additional mCPBA (1.5 g, 6.1 mmol) was added, and the reaction was stirred overnight. The reaction was not washed prior to the addition of ammonium hydroxide. The amination reaction was stirred for two hours. The extraction was carried out with dichloromethane (10 x 50 mL). The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 95:5 to 80:20), recrystallized from ethanol:water, and dried overnight in a vacuum oven at 70 °C to provide 0.417 g of 3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2,2-dimethylpropionamide as tan crystals, mp 241-243 °C.

Anal. Calcd for $C_{18}H_{23}N_5O_2$: C, 63.32; H, 6.79; N, 20.51. Found: C, 63.21; H, 7.08; N, 20.62.

Example 29

4-(4-Amino-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one

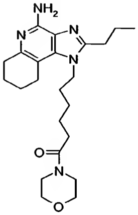


A mixture of 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one (0.62 g, 1.6 mmol, prepared as described in Example 1), platinum (IV) oxide (0.25 g, 1.1 mmol), and trifluoroacetic acid (25 mL) was placed in a Parr vessel and shaken under hydrogen pressure (50 psi, 3.5×10^5 Pa) for two hours. An analysis by LC/MS indicated the reaction was incomplete. Additional platinum (IV) oxide (0.5 g) was added, and the reaction was continued overnight. The trifluoroacetic acid was removed under reduced pressure, and the residue was dissolved in methanol (35 mL). Aqueous sodium hydroxide (10 mL of 25%) was added to the solution, and the mixture was stirred for 15 minutes and then diluted with dichloromethane (100 mL). The mixture was filtered through a layer of CELITE filter aid, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with 5% aqueous sodium hydroxide (2 x 25 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure. The resulting solid was recrystallized from water:acetonitrile; the crystals were triturated with 25% aqueous sodium hydroxide for one hour, diluted with water, isolated by filtration, and recrystallized from water:ethanol. The resulting crystals were dried overnight in a vacuum oven at 70 °C to provide 0.5706 g of 4-(4-amino-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylbutan-1-one as white crystals, mp 181-183 °C.

Anal. Calcd for $C_{21}H_{31}N_5O_2$: C, 65.43; H, 8.11; N, 18.17. Found: C, 65.36; H, 8.40; N, 18.11.

Example 30

6-(4-Amino-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one



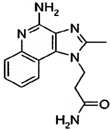
A second batch of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one was prepared according to the methods described in Example 6 with the following modifications. In Part C, a solution of ethyl 6-(3-nitroquinolin-4-ylamino)hexanoate (122.94 g, 371.6 mmol) in dichloromethane (800 mL) was added to a solution of sodium hydrosulfite (226.44 g, 1.30 mol), potassium carbonate (202.86 g, 1.47 mol), and ethyl viologen diiodide (1.737 g, 3.71 mmol) in water (800 mL), and the reaction was stirred overnight at ambient temperature. The organic layer was separated, washed with water (4 x), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 106.7 g of 6-(3-aminoquinolin-4-ylamino) ethyl hexanoate. The crude product from Part G was recrystallized from methanol, triturated with hot ethyl acetate twice, triturated with hexanes, and isolated by filtration to provide 20.9 g of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one as a light tan powder, mp 156-158 °C.

A mixture of 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one (2.0 g, 4.9 mmol), platinum (IV) oxide (1.5 g, 6.6 mmol), and trifluoroacetic acid (50 mL) was placed in a Parr vessel and shaken under hydrogen pressure (50 psi, 3.5×10^5 Pa) for 24 hours. The trifluoroacetic acid was removed under reduced pressure, and the residue was sonicated with 10% aqueous sodium hydroxide. The resulting solid was mixed with material from another run and recrystallized from water. The crystals were isolated by filtration and dried overnight at 80 °C to provide

0.978 g of 6-(4-amino-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylhexan-1-one as a white crystaline powder, mp 162-163 °C.
Anal. Calcd for $C_{23}H_{35}N_5O_2$: C, 66.80; H, 8.53; N, 16.93. Found: C, 66.54; H, 8.85; N, 16.87.

Example 31

3-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide



Part A

Ammonium acetate (4.0 g) and ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (4.5 g, 17 mmol, prepared as described in Parts A through C of Example 22) were heated for three days at 130 °C in a sealed vessel. The reaction was allowed to cool to ambient temperature, and water was added. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 90:10 to 85:15) to provide 2.20 g of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide as a tan solid.

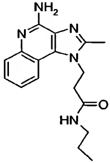
Part B

mCPBA (3.48 g, 15.1 mmol) was added to a solution of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide (2.20 g, 8.65 mmol) in chloroform (100 mL). The reaction was stirred for two hours at ambient temperature and cooled to 0 °C. Ammonium hydroxide (40 mL) was added followed by *p*-toluenesulfonyl chloride (3.21 g, 16.9 mmol), which was added over a period of five minutes. The reaction was stirred for two hours at ambient temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 90:10 to 80:20). The resulting solid was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven at 60 °C to provide 0.145 g of 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide as a off-white powder, mp 237-239 °C.

Anal. Calcd for $C_{14}H_{15}N_5O$: C, 57.78; H, 6.03; N, 24.06. Found: C, 57.38; H, 5.82; N, 24.29.

Example 32

3-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide



Part A

Ethyl 3-(3-nitroquinolin-4-ylamino)propionate (62.0 g, 214 mmol, prepared as described in Part A of Example 22) was treated with sodium hydrosulfite (130.59 g, 750.04 mmol), potassium carbonate (117 g, 847 mmol), and ethyl viologen dibromide (0.802 g, 2.14 mmol) according to a modification of the method described in Part A of Example 8. After the reaction was stirred overnight, additional water (100 mL), dichloromethane (100 mL) and sodium hydrosulfite (20.0 g, 11.5 mmol) were added, and the reaction was stirred for three additional hours. The organic layer was separated; washed sequentially with water, saturated aqueous sodium bicarbonate, and brine; dried over magnesium sulfate; filtered; and concentrated under reduced pressure to provide 40.2 g of 3-(3-aminoquinolin-4-ylamino) ethyl propionate.

Part B

3-(3-Aminoquinolin-4-ylamino) ethyl propionate (9.0 g, 35 mmol) was treated with triethyl orthoacetate (8.91 mL, 48.6 mmol) and pyridinium *p*-toluenesulfonate (0.200 g) according to the method described in Part A of Example 10 to provide 6.10 g of ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate. The reaction was complete in two hours, and a precipitate was removed by filtration from the organic layer during the work-up procedure.

Part C

Propylamine (20 mL) and ethyl 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (5.77 g, 20.4 mmol) were heated overnight at 100 °C in a sealed vessel. The reaction was allowed to cool to ambient temperature and concentrated under reduced pressure to provide 6.0 g of 3-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide.

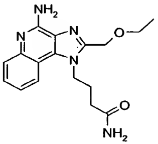
Part D

3-(2-Methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide (6.0 g, 20.2 mmol) was treated with mCPBA (8.15 g, 35.4 mmol) followed by ammonium hydroxide (40 mL) and *p*-toluenesulfonyl chloride (7.52 g, 39.5 mmol) according to a modification of the method described in Part D of Example 8. The reaction was not washed with 10% aqueous sodium hydroxide prior to the addition of ammonium hydroxide. The crude product was twice triturated with ethyl acetate and isolated by filtration. The solid was then purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol). The product was then triturated sequentially with 10% aqueous sodium hydroxide and acetone (2 x). The solid was then purified again by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 95:5 to 90:10). The resulting solid was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight to provide 0.477 g of 3-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylpropionamide as an off-white powder, mp 188-189 °C.

Anal. Calcd for $C_{17}H_{21}N_5O$: C, 65.57; H, 6.80; N, 22.49. Found: C, 65.24; H, 6.67; N, 22.44.

Example 33

4-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide



Part A

4-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl) ethyl butyrate (15.9 g, 46.6 mmol, prepared as described in Parts A through C of Example 5) and ammonium acetate

(35.0 g, 455 mmol) were sealed and heated in a high-pressure vessel at 130 °C for two days. An analysis by LC/MS indicated the presence of starting material, and additional ammonium acetate (15 g, 190 mmol) was added. The reaction was heated to 130 °C for several hours, allowed to cool to ambient temperature, stirred for three days, and poured into water (200 mL). Solid sodium bicarbonate was added until the solution was basic. The solution was extracted with dichloromethane (3 x 100 mL, 5 x 75 mL, and then in a continuous extractor for about 20 hours). The extracts were dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 10.3 g of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide as a light yellow solid.

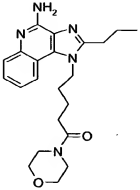
Part B

4-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide (4.3 g, 14 mmol) was treated with mCPBA (6.1 g, 27 mmol), concentrated ammonium hydroxide (50 mL of 29%), and *p*-toluenesulfonyl chloride (4.6 g, 24 mmol) according to a modification of the method described in Part E of Example 3. The mCPBA addition was carried out at 0 °C, and the reaction was carried out in dichloromethane (150 mL). At the end of the reaction the layers were separated, and saturated aqueous sodium bicarbonate (100 mL) and 5% aqueous sodium hydroxide (10 mL) were added to the organic layer. The aqueous layer was extracted with dichloromethane (1.3 L), and the combined extracts were dried over potassium carbonate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol containing 4 mL/L of ammonium hydroxide) followed by recrystallization five times from ethanol containing a small amount of water. The resulting solid was recrystallized from water:acetonitrile (5:1), dried overnight in a vacuum oven at 70 °C, triturated with 25% aqueous ammonium hydroxide, diluted with water, isolated by filtration, recrystallized from ethanol:water, and dried overnight in a vacuum oven at 70 °C to provide 0.4704 g of 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide as tan crystals, mp 233-235 °C.

Anal. Calcd for $C_{17}H_{21}N_5O_2 \cdot 0.07\ H_2O$: C, 62.12; H, 6.48; N, 21.31. Found: C, 61.77; H, 6.83; N, 21.22.

Example 34

5-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one



Part A

Potassium carbonate (66.23 g, 479.3 mmol), triethylamine (167 mL, 1.20 mol), and ethyl 5-aminovalerate hydrochloride (104.4 g, 575.2 mmol) were added to a solution of 4-chloro-3-nitroquinoline (100.0 g, 479.3 mmol) in chloroform (1000 mL) according to the method described in Part B of Example 6. The reaction was run for four hours and provided 151 g of ethyl 5-(3-nitroquinolin-4-ylamino)pentanoate.

Part B

A solution of ethyl 5-(3-nitroquinolin-4-ylamino)pentanoate (151 g, 476 mmol) in dichloromethane (1 L) was added to a solution of sodium hydrosulfite (248.5 g, 1.427 mol), potassium carbonate (259.3 g, 1.876 mol), and ethyl viologen dibromide (1.78 g, 4.75 mmol) in water (1 L), and the reaction was stirred overnight at ambient temperature. An analysis by TLC indicated the presence of starting material; additional sodium hydrosulfite (5.0 g, 29 mmol) was added to the reaction, which was stirred for one additional hour. The organic layer was separated, washed with water (3 x), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 131.51 g of 5-(3-aminoquinolin-4-ylamino) ethyl pentanoate.

Part C

The method described in Part A of Example 10 was used to treat 5-(3-aminoquinolin-4-ylamino) ethyl pentanoate (26.3 g, 91.5 mmol) with trimethyl orthobutyrate (18.3 mL, 114 mmol) and pyridinium *p*-toluenesulfonate (0.5 g). The reaction was complete in three hours to provide 28 g of ethyl 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate as a brown oil.

Part D

A solution of sodium hydroxide (2.23 g, 55.9 mmol) in water (100 mL) was added to a solution of ethyl 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (14.6 g, 43.0 mmol) in ethanol (100 mL), and the reaction was stirred at ambient temperature overnight, concentrated to remove ethanol, and washed with dichloromethane. The resulting solution was adjusted to pH 5 with the addition of 10% hydrochloric acid. The mixture was extracted twice with chloroform, and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 11.5 g of 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoic acid.

Part E

A modification of the method described in Part F of Example 6 was used to treat 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoic acid (5.14 g, 16.5 mmol) with oxalyl chloride (2.59 mL, 29.7 mmol) and morpholine (4.33 mL, 49.5 mmol). The oxalyl chloride addition was carried out at ambient temperature, and the reaction with morpholine was complete in three hours. Following the work-up procedure, 6.2 g of 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one were obtained.

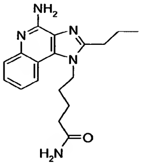
Part F

mCPBA (6.56 g, 28.5 mmol) was added to a solution of 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one (6.2 g, 16 mmol) in chloroform (100 mL); the reaction was stirred for three hours at ambient temperature. Ammonium hydroxide (50 mL) was added. *p*-Toluenesulfonyl chloride (6.056 g, 31.76 mmol) was added over a period of five minutes, and the reaction was stirred for one hour. The work-up procedure and chromatographic purification was carried out as described in Part D of Example 8. The resulting oil was triturated with acetone, isolated by filtration, and dried to provide 5-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one as a tan powder, mp 178-179 °C.

Anal. Calcd for $C_{22}H_{29}N_5O_2$: C, 66.81; H, 7.391; N, 17.71. Found: C, 66.50; H, 7.38; N, 17.41.

Example 35

5-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide



Part A

Ethyl 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (5.4 g, 15.9 mmol), prepared as described in Parts A through C of Example 34) and ammonium acetate (11.0 g, 143 mmol) were sealed in a high-pressure vessel and heated for two days at 130 °C and then allowed to cool to ambient temperature. Ammonium hydroxide was added to adjust the mixture to a neutral pH. The mixture was then extracted with dichloromethane, and the combined extracts were washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 2.8 g of 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide, which was combined with material from another run.

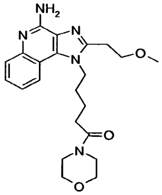
Part B

5-(2-Propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide (4.4 g, 14 mmol) was treated with mCPBA (4.28 g, 24.8 mmol), ammonium hydroxide (40 mL), and *p*-toluenesulfonyl chloride (5.24 g, 27.4 mmol) according to a modification of the method described in Part F of Example 34. At the completion of the amination reaction, a precipitate was present and was isolated by filtration. The precipitate was triturated and sonicated with acetone, isolated by filtration, and dried in a vacuum oven at 80 °C to provide 1.28 g of 5-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide as a tan powder, mp 202-203 °C.

Anal. Calcd for $C_{18}H_{23}N_5O \cdot 0.09\ H_2O$: C, 66.09; H, 7.15; N, 21.41. Found: C, 65.69; H, 7.46; N, 21.22.

Example 36

5-[4-Amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylpentan-1-one



Part A

5-(3-Aminoquinolin-4-ylamino) ethyl pentanoate (23.0 g, 88.6 mmol, prepared in Parts A and B of Example 34) was treated according to the method described in Part A of Example 12. The addition of methoxypropionyl chloride (12.97 g, 106.3 mmol) was carried out at 0 °C, and the reaction was stirred at ambient temperature for two hours. The reaction with triethylamine (49.4 g, 354 mmol) was heated at reflux for four hours. After the work-up procedure, 28.6 g of ethyl 5-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanoate were obtained as a brown oil.

Part B

Ethyl 5-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanoate (15.1 g, 42.4 mmol) was treated with sodium hydroxide (2.20 g, 55.2 mmol) according to the method described in Part A of Example 11. The reaction was stirred overnight at ambient temperature to provide 10.2 g of 5-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanoic acid after the aqueous work-up procedure.

Part C

5-[2-(2-Methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentanoic acid (5.5 g, 17 mmol) was treated according to a modification of the method described in Part F of Example 6. The reaction with oxalyl chloride (2.63 mL, 30.2 mmol) was carried out at ambient temperature and was complete in 30 minutes. The reaction with morpholine (4.40 mL, 50.4 mmol) was complete after 30 minutes. Following the work-up procedure, 6.5 g

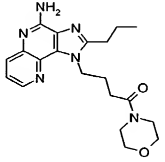
of 5-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylpentan-1-one were obtained.

Part D

mCPBA (6.60 g, 28.7 mmol) was added to a solution of 5-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylpentan-1-one (6.5 g, 17 mmol) in chloroform (100 mL); the reaction was stirred for two hours at ambient temperature. The reaction was cooled to 0 °C, and ammonium hydroxide (50 mL) was added. A solution of benzenesulfonyl chloride (4.11 mL, 33.0 mmol) in chloroform (20 mL) was added over a period of 20 minutes, and the reaction was allowed to warm to ambient temperature and stirred for two hours. The work-up procedure and chromatographic purification was carried out as described in Part D of Example 8. The resulting product was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide 5-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1-morpholin-4-ylpentan-1-one as an off-white powder, mp 128-129 °C. Anal. Calcd for $C_{22}H_{29}N_5O_3 \cdot 0.17\ H_2O$: C, 63.74; H, 7.13; N, 16.89. Found: C, 63.33; H, 7.34; N, 16.73.

Example 37

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylbutan-1-one



Part A

A suspension of 4-chloro-3-nitro[1,5]naphthyridine (10.0 g, 47.7 mmol) and ethyl 4-aminobutyrate hydrochloride (9.6 g, 57 mmol) in dichloromethane (200 mL) was cooled to 5 °C. Triethylamine (16.6 mL, 119 mmol) was added, and the reaction was allowed to warm to ambient temperature and stirred for two hours. The mixture was diluted with

dichloromethane (200 mL) and washed with saturated aqueous sodium bicarbonate (2 x 150 mL). The combined aqueous fractions were extracted with dichloromethane (100 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 14.5 g of ethyl 4-(3-nitro[1,5]naphthyridin-4-ylamino)butyrate as a yellow solid.

Part B

A mixture of ethyl 4-(3-nitro[1,5]naphthyridin-4-ylamino)butyrate (5.0 g, 16 mmol), 5% platinum on carbon (0.50 g), and ethyl acetate (80 mL) was added to a Parr vessel, and the reaction was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) for 2.5 hours. The reaction mixture was filtered through a layer of CELITE filter agent, and the filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to provide 4-(3-amino[1,5]naphthyridin-4-ylamino) ethyl butyrate as a yellow oil.

Part C

A solution of 4-(3-amino[1,5]naphthyridin-4-ylamino) ethyl butyrate (2.0 g, 7.3 mmol) in dichloromethane (35 mL) was cooled to 0 °C. Butyryl chloride (0.68 mL, 8.0 mmol) was added dropwise over a period of ten minutes, and the reaction was allowed to warm to ambient temperature, stirred for 90 minutes, and concentrated under reduced pressure. Triethylamine (3.0 mL, 22 mmol) and ethanol (35 mL) were added, and the resulting solution was heated at reflux for two days. Pyridine hydrochloride (0.1 equivalents) was added, and the reaction was heated at reflux overnight. The solvent was removed under reduced pressure, and the residue was partitioned between dichloromethane (70 mL) and saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was separated and extracted with dichloromethane (2 x 25 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 2.43 g of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyrate as a brown oil.

Part D

Aqueous sodium hydroxide (2.4 mL of 6 M) was added to a solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyrate (2.37 g, 7.26 mmol) in ethanol (25 mL); the reaction was stirred at ambient temperature for two hours and concentrated under reduced pressure. The residue was dissolved in water (15 mL) and adjusted to pH 4

with the addition of 2 M hydrochloric acid. A precipitate formed, was isolated by filtration, and was mixed with toluene, which was removed under reduced pressure to provide 1.78 g of 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyric acid as a tan powder.

Part E

4-(2-Propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyric acid (prepared in a separate run, 5.34 mmol) was treated according to a modification of Part F of Example 6. One drop of DMF was added to the reaction mixture. The addition of oxalyl chloride (1.4 mL, 16 mmol) was carried out at ambient temperature, and the reaction was stirred for two hours. Additional oxalyl chloride (0.5 mL) was added, and the reaction was stirred for an additional hour. The reaction with morpholine (1.17 mL, 13.3 mmol) was stirred for one hour. Following the work-up procedure 1.80 g of 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylbutan-1-one were obtained as a yellow solid.

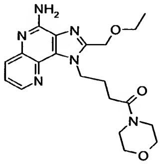
Part F

mCPBA (1.18 g, 6.86 mmol) was added to a solution of 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylbutan-1-one (1.80 g, 4.90 mmol) in chloroform (25 mL); the reaction was stirred for two hours at ambient temperature. Ammonium hydroxide (10 mL) was added followed by *p*-toluenesulfonyl chloride (1.03 g, 5.39 mmol). The reaction was stirred for one hour and partitioned between saturated aqueous sodium bicarbonate (75 mL) and dichloromethane (70 mL). The aqueous layer was extracted with dichloromethane (2 x 25 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting brown solid was triturated twice with acetonitrile and then purified on a Biotage HORIZON High-Performance Flash Chromatography (HPFC) instrument (FLASH 40+M cartridge). The polar component of the eluent was chloroform:methanol:ammonium hydroxide 80:18:2 (CMA). The purification was carried out eluting with chloroform:CMA in a gradient from 100:0 to 75:25. The resulting solid was dried under high vacuum at 80 °C to provide 0.583 g of 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylbutan-1-one as an off-white powder, mp 196-197 °C.

Anal. Calcd for $C_{20}H_{26}N_6O_2$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.60; H, 7.06; N, 22.00.

Example 38

4-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylbutan-1-one



Part A

Ethyl 4-(3-amino[1,5]naphthyridin-4-ylamino)butyrate (2.5 g, 9.1 mmol, prepared in Parts A and B of Example 37) was treated with ethoxyacetyl chloride (1.02 mL, 10.0 mmol) and cyclized according to a modification of the method described in Part C of Example 37. The reaction with triethylamine (3.8 mL, 27 mmol) was heated at reflux overnight and was complete. Following the work-up procedure, 3.11 g of ethyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyrate were obtained as a brown oil.

Part B

The methods of Parts D and E of Example 37 were used to treat ethyl 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyrate (1.0 g, 2.9 mmol) with aqueous sodium hydroxide (2.9 mL of 2 M), oxalyl chloride (0.42 mL, 4.8 mmol), and morpholine (0.35 mL, 4.0 mmol). The reaction with oxalyl chloride was complete within two hours, and no additional reagent was added. Following the work-up procedure 0.64 g of 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylbutan-1-one was obtained as a yellow solid, which was combined with material from another run.

Part C

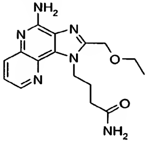
The method described in Part F of Example 37 was used to treat 4-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylbutan-1-one (1.42 g, 3.70 mmol) with mCPBA (0.958 g, 5.55 mmol), ammonium hydroxide (4 mL), and *p*-toluenesulfonyl chloride (0.776 g, 4.07 mmol). Following the chromatographic purification, the resulting solid was dried for 48 hours under high vacuum at 120 °C to provide 0.614 g of 4-(4-

amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylbutan-1-one as a tan powder, mp 156-157 °C.

Anal. Calcd for $C_{20}H_{26}N_6O_3 \cdot 0.3H_2O$: C, 59.48; H, 6.64; N, 20.81. Found: C, 59.55; H, 6.63; N, 20.70.

Example 39

4-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyramide



Part A

A solution of ammonia in dioxane (33 mL of 0.5 M) was added to a solution of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyryl chloride (4.64 mmol, prepared as described in Parts A and B of Example 38) in dichloromethane (20 mL), and the reaction was stirred overnight at ambient temperature. An analysis by HPLC indicated the reaction was incomplete; ammonia gas was bubbled through the solution for 10 minutes. The reaction was then stirred for one hour and concentrated under reduced pressure. The residue was triturated with water and isolated by filtration to provide 1.02 g of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyramide. The filtrate was extracted with dichloromethane (3 x 20 mL), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide an additional 0.39 g of product. The combined solids were mixed with material from another run.

Part B

mCPBA (1.80 g, 7.28 mmol) was added to a solution of 4-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyramide (1.63 g, 5.20 mmol) in chloroform (50 mL); the reaction was stirred for three hours at ambient temperature. An analysis by LC/MS indicated the reaction was incomplete; therefore, additional mCPBA (1.2 equivalents) was added. The reaction was stirred for two hours and then diluted with

saturated aqueous sodium bicarbonate (75 mL) and chloroform (75 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL) and chloroform (12 x 20 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 2.34 g of 4-(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyramide as an orange solid.

Part C

A solution of the material from Part B in methanol (25 mL) was cooled to 0 °C; ammonium hydroxide (1.8 mL, 26 mmol) was added. Benzenesulfonyl chloride (1.3 mL, 10.4 mmol) was added dropwise, and the reaction was stirred for one hour at 0 °C and concentrated under reduced pressure. The residue was triturated with methanol, isolated by filtration, and dissolved in aqueous sodium hydroxide (20 mL of 2 M). The solution was sonicated to form a precipitate, which was isolated by filtration, washed with cold water, and dried overnight in a vacuum oven at 80 °C to provide 0.432 g of 4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyramide as a pale yellow powder, mp 231-232 °C.

Anal. Calcd for $C_{16}H_{20}N_6O_2 \cdot 0.3H_2O$: C, 57.58; H, 6.22; N, 25.18. Found: C, 57.76; H, 6.39; N, 25.12.

Examples 40-45

Part A

Under a nitrogen atmosphere, triethylamine (47 mL, 340 mmol) was added to a solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (30.0 g, 136 mmol) and ethyl 4-aminobutyrate hydrochloride (32 g, 190 mmol) in *N,N*-dimethylformamide (DMF) (500 mL), and the reaction was stirred overnight. The solvent was removed under reduced pressure, and the residue was partitioned between chloroform (500 mL), water (25 mL), and brine (25 mL). The organic layer was separated and washed with water:brine (1:1, 3 x 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting orange solid was recrystallized from ethyl acetate:hexanes and dried under high vacuum to provide 21.5 g of 4-(2-chloro-5,6-dimethyl-3-nitropyridin-4-ylamino) ethyl butyrate.

Part B

Under a nitrogen atmosphere, a mixture of 4-(2-chloro-5,6-dimethyl-3-nitropyridin-4-ylamino) ethyl butyrate (21.5 g, 68 mmol), sodium azide (8.90 g, 136 mmol), cerium(III) chloride heptahydrate (12.7 g, 34 mmol), and 9:1 acetonitrile:water (250 mL) was heated overnight at reflux. The hot reaction mixture was filtered, and the filter cake was washed with acetonitrile. The filtrate was concentrated under reduced pressure, and the residue was triturated with ethyl acetate:hexanes and isolated by filtration to provide 21.5 g of 4-(5,6-dimethyl-8-nitrotetrazolo[1,5-*a*]pyridin-7-ylamino) ethyl butyrate.

Part C

A mixture of 4-(5,6-dimethyl-8-nitrotetrazolo[1,5-*a*]pyridin-7-ylamino) ethyl butyrate (10.0 g, 31.0 mmol), 10% palladium on carbon (1.0 g), and acetonitrile (310 mL) was added to a pressure vessel, and the reaction was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) overnight. The reaction mixture was filtered through a layer of CELITE filter agent, and the filter cake was washed with methanol (50 mL). The filtrate was concentrated under reduced pressure to provide 4-(8-amino-5,6-dimethyltetrazolo[1,5-*a*]pyridin-7-ylamino) ethyl butyrate as a solid. This reaction was repeated a second time.

Part D

For Examples 40 and 41, pyridine hydrochloride (1.34 g, 11.6 mmol) and trimethyl orthobutyrate (5.42 mL, 34.1 mmol) were sequentially added with stirring to a solution of 4-(8-amino-5,6-dimethyltetrazolo[1,5-*a*]pyridin-7-ylamino) ethyl butyrate (9.1 g, 31 mmol) in toluene (310 mL) under a nitrogen atmosphere. The reaction was heated at reflux for 1.5 hours, allowed to cool to ambient temperature overnight, and concentrated under reduced pressure. The residue was partitioned between chloroform (300 mL) and saturated aqueous sodium bicarbonate (75 mL). The aqueous layer was extracted with chloroform (2 x 100 mL), and the combined organic fractions were washed with saturated aqueous sodium bicarbonate (2 x 75 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was triturated with ethyl acetate and isolated by filtration to provide 6.0 g of 4-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)butyrate as a white solid.

For Examples 42 and 43, pyridine hydrochloride (668 mg, 5.78 mmol) and triethyl orthopropionate (3.4 mL, 17 mmol) were added to a solution of 4-(8-amino-5,6-dimethyltetrazolo[1,5-*a*]pyridin-7-ylamino) ethyl butyrate (4.5 g, 15 mmol) in toluene

(100 mL). The reaction and work-up procedure were as described for Examples 40 and 41. The crude product was recrystallized from ethyl acetate:hexane, isolated by filtration, washed with ethyl acetate:hexane, and dried under high vacuum to provide 4.7 g of 4-(5,6-dimethyl-8-ethyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)butyrate as off-white crystals.

For Examples 44 and 45, a solution of 4-(8-amino-5,6-dimethyltetrazolo[1,5-*a*]pyridin-7-ylamino) ethyl butyrate (4.5 g, 15 mmol) in dichloromethane (150 mL) was cooled to 0 °C under a nitrogen atmosphere. Ethoxyacetyl chloride (2.46 g, 18.5 mmol) was added dropwise, and the reaction was allowed to warm to ambient temperature and stirred for four hours. Additional ethoxyacetyl chloride (0.5 g) was added, and the reaction was stirred for three days. Additional ethoxyacetyl chloride (1.0 g) was again added, and the reaction was stirred for two hours and concentrated under reduced pressure.

Part E

For Examples 40-43, aqueous sodium hydroxide (2.0 equivalents of 2 M or 6 M) was added dropwise to a suspension of the material from Part D in ethanol (0.2 M) under a nitrogen atmosphere. The reaction was stirred for one hour and concentrated under reduced pressure. The residue was dissolved in a small amount of water (5-8 mL), and the resulting solution was adjusted to pH 4 with the addition of 2 M hydrochloric acid. A precipitate formed and was isolated by filtration, washed with water, and optionally mixed with toluene, which was removed under reduced pressure. The resulting solid was dried under vacuum for two to several hours, optionally at 60-70 °C.

For Examples 44 and 45, aqueous sodium hydroxide (39 mL of 2 M) was added dropwise to a suspension of the material from Part D in ethanol (154 mL), and the reaction was heated at 60 °C under nitrogen for two hours. The reaction was allowed to cool to ambient temperature, adjusted to pH 7 with the addition of 1 N hydrochloric acid, and allowed to stand overnight. The solvent was removed under reduced pressure. Toluene (50 mL) and methanol (10 mL) were twice added and removed under reduced pressure. The residue was dried under high vacuum, mixed with methanol (200 mL), and filtered to remove sodium chloride. The filter cake was washed with methanol, and the filtrate was concentrated under reduced pressure to provide a solid.

Part F

Under a nitrogen atmosphere, oxalyl choride (3.0 equivalents) was added dropwise over a period of five minutes to a suspension of the butyric acid from Part E in dichloromethane (0.1 M) and four drops of DMF. The reaction was stirred for one hour, and additional oxalyl chloride (0.5 mL) was added in Examples 40, 41, 44, and 45. The solvent was removed under reduced pressure.

Part G

For Examples 40, 42, and 44, a suspension of the acid chloride from Part F in dichloromethane (0.1 M) was cooled to 0 °C under a nitrogen atmosphere. Ammonia (1.5 equivalents of a 0.5 M solution in dioxane) was added dropwise over a period of five minutes. The reaction was stirred for ten minutes, and then ammonia gas was bubbled through the solution for ten minutes. The reaction was stirred overnight at ambient temperature and concentrated under reduced pressure. The residue was triturated with water (Example 40 and 44) or water:ethyl acetate (Example 42), isolated by filtration, washed with water or water:ethyl acetate, and dried under vacuum for two to three hours optionally at 70 °C to provide the amide product as a solid.

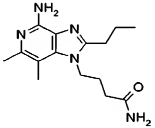
For Examples 41, 43, and 45, a suspension of the acid chloride from Part F in dichloromethane (0.1 M) was cooled to 0 °C under a nitrogen atmosphere. Morpholine (6.0 equivalents) was added dropwise over a period of five minutes, and the reaction was stirred overnight at ambient temperature. The solvent was removed under reduced pressure. For Example 41, the residue was triturated with ethyl acetate (30 mL) and methanol (5 mL), and the resulting solid was isolated by filtration, washed with ethyl acetate, and partitioned between chloroform (100 mL) and saturated aqueous sodium bicarbonate (40 mL). The aqueous layer was separated and extracted with chloroform (2 x 50 mL), and the combined organic fractions were washed with saturated aqueous sodium bicarbonate (2 x 30 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a white solid. For Example 43, the residue was triturated with ethyl acetate:water, and the resulting solid was isolated by filtration, washed with ethyl acetate and water, and dried in a vacuum oven for one hour at 70 °C. For Example 45, the residue was subjected to the aqueous work-up procedure described for Example 41. The resulting solid was triturated with ethyl acetate, isolated by filtration, washed with ethyl acetate, and dried under high vacuum to provide a white solid.

Part H

A pressure vessel was charged with the material from Part G, platinum (IV) oxide (20 wt.%), and trifluoroacetic acid (0.1 M), and the mixture was placed under hydrogen pressure (50 psi, 3.4×10^5 Pa) and shaken over three days. The reaction mixture was filtered, optionally through a pad of CELITE filter agent (Example 40), and the filter cake was washed with methanol. The filtrate was concentrated under reduced pressure, and the residue was mixed with 1 N hydrochloric acid (5-10 mL), stirred for between 1.5 and three hours, cooled to 0 °C, and optionally diluted with chloroform (20-30 mL). The resulting mixture was made basic with the addition of 6 N sodium hydroxide (Examples 40, 42, and 43), 6 N aqueous potassium carbonate (Examples 44 and 45), or saturated aqueous sodium bicarbonate (Example 41). For Examples 40 and 42, a precipitate formed, was isolated by filtration, dissolved in methanol, and concentrated under reduced pressure. For Examples 41 and 43-45, the aqueous layer was separated and extracted with chloroform (3 x 50 mL). The combined organic fractions were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The purification and characterization is given below for each product.

Example 40

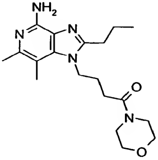
4-(4-Amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyramide



The product was triturated with ethyl acetate, isolated by filtration, triturated with methanol, isolated by filtration, washed with methanol and acetonitrile, and dried overnight under high vacuum at 80 °C to provide 4-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyramide as a white powder, mp 226.0-228.0 °C.
Anal. Calcd for $C_{15}H_{23}N_5O$: C, 62.26; H, 8.01; N, 24.20; Found: C, 61.99; H, 8.07; N, 24.36.

Example 41

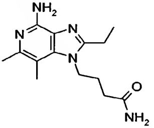
4-(4-Amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-1-morpholin-4-ylbutan-1-one



The product was purified by HPFC (eluting with chloroform:CMA in a gradient from 95:5 to 60:40) followed by recrystallization from ethyl acetate. The crystals were dried under high vacuum to provide 4-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-1-morpholin-4-ylbutan-1-one as a white powder, mp 164.0-165.0 °C. Anal. Calcd for $C_{19}H_{29}N_5O_2$: C, 63.48; H, 8.13; N, 19.48. Found: C, 63.30; H, 8.33; N, 19.49.

Example 42

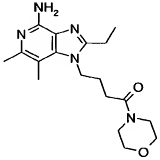
4-(4-Amino-6,7-dimethyl-2-ethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyramide



The product was triturated with acetonitrile, isolated by filtration, triturated with 1 N sodium hydroxide, isolated by filtration, washed with water, triturated with ethyl acetate, and dried under high vacuum with stirring at 100 °C for three hours to provide 4-(4-amino-6,7-dimethyl-2-ethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyramide as a white powder, mp 228.0-230.0 °C.
Anal. Calcd for $C_{14}H_{21}N_5O \cdot 0.09H_2O$: C, 60.71; H, 7.71; N, 25.29. Found: C, 60.45; H, 8.07; N, 25.56.

Example 43

4-(4-Amino-6,7-dimethyl-2-ethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-1-morpholin-4-ylbutan-1-one

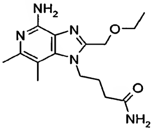


The product was triturated with ethyl acetate, dried under high vacuum, recrystallized twice from acetonitrile, isolated by filtration, washed with acetonitrile, and dried under high vacuum with stirring at 100 °C for three hours to provide 4-(4-amino-6,7-dimethyl-2-ethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-1-morpholin-4-ylbutan-1-one as a white powder, mp 209.0-210.0 °C.

Anal. Calcd for $C_{18}H_{27}N_5O_2$: C, 62.59; H, 7.88; N, 20.27. Found: C, 62.49; H, 8.09; N, 20.34.

Example 44

4-(4-Amino-6,7-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyramide

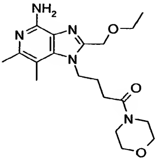


The product was triturated with ethyl acetate, isolated by filtration, washed with ethyl acetate, sonicated with 1 N sodium hydroxide for one minute, isolated by filtration, washed with water, and dried under high vacuum overnight to provide 4-(4-amino-6,7-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyramide as a white powder, mp 199.0-200.0 °C.

Anal. Calcd for $C_{15}H_{23}N_5O_2$: C, 59.00; H, 7.59; N, 22.93. Found: C, 58.72; H, 7.53; N, 22.76.

Example 45

4-(4-Amino-6,7-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-1-morpholin-4-ylbutan-1-one

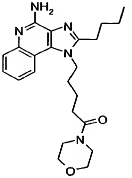


The product was triturated with ethyl acetate, isolated by filtration, washed with ethyl acetate, sonicated with 1 N sodium hydroxide (5 mL) for 30 seconds, and diluted with water (20 mL) and chloroform (50 mL). The aqueous layer was separated and extracted with chloroform (3 x 20 mL). The combined organic fractions were washed with 1 N sodium hydroxide (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with ethyl acetate, isolated by filtration, and dried under high vacuum for two hours at 70 °C to provide 4-(4-amino-6,7-dimethyl-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-1-morpholin-4-ylbutan-1-one as a white powder, mp 156.0-158.0 °C.

Anal. Calcd for $C_{19}H_{29}N_5O_3$: C, 60.78; H, 7.785; N, 18.65. Found: C, 60.44; H, 8.07; N, 18.32.

Example 46

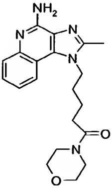
5-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one



The methods described in Parts C, D, E, and F of Example 34 were used to treat 5-(3-aminoquinolin-4-ylamino) ethyl pentanoate, prepared in Parts A and B of Example 34. Trimethyl orthovalerate was used instead of trimethyl orthobutyrate in Part C. Following chromatographic purification of the product from Part F (eluting with 95:5 dichloromethane:methanol), 5-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one was obtained as an off-white powder, mp 141-143 °C. Anal. Calcd for $C_{23}H_{31}N_5O_2$: C, 67.46; H, 7.63; N, 17.10. Found: C, 67.37; H, 7.66; N, 16.90.

Example 47

5-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one



Part A

The methods described in Parts C, D, and E of Example 34 were used to convert 5-(3-aminoquinolin-4-ylamino) ethyl pentanoate, prepared in Parts A and B of Example 34, to 5-(2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one.

Trimethyl orthoacetate was used instead of trimethyl orthobutyrate in Part C, and the reaction was heated for four hours. In Part E, the treatment with oxalyl chloride (1.8 equivalents) was carried out three times for 15 minutes each time. DMF (5 mL) was added to the reaction before the first addition.

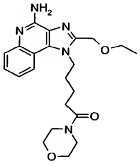
Part B

5-(2-Methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one (8.4 g, 24 mmol) was treated with mCPBA (7.19 g, 41.7 mmol), ammonium hydroxide (40 mL), and benzenesulfonyl chloride (5.93 mL, 46.5 mmol) according to the method described in Part D of Example 36. The crude product was purified by column chromatography on silica gel (eluting with 90:10 dichloromethane:methanol). The resulting product was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide 0.487 g of 5-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one as an off-white powder, mp 218-219 °C.

Anal. Calcd for $C_{20}H_{25}N_5O_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.20; H, 7.03; N, 18.98.

Example 48

5-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one



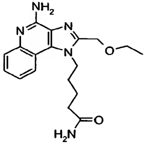
The methods described in Parts A through D of Example 36 were used to treat 5-(3-aminoquinolin-4-ylamino) ethyl pentanoate, prepared in Parts A and B of Example 34. Ethoxyacetyl chloride was used instead of methoxypropionyl chloride in Part A. Following chromatographic purification of the product from Part D (eluting with 95:5 dichloromethane:methanol), the product was triturated with 10% sodium hydroxide,

isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one as a tan solid, mp 128-129 °C.

Anal. Calcd for $C_{22}H_{29}N_5O_3 \cdot 0.54H_2O$: C, 62.72; H, 7.20; N, 16.62. Found: C, 62.72; H, 7.16; N, 16.60.

Example 49

5-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide



Part A

5-(3-Aminoquinolin-4-ylamino) ethyl pentanoate, prepared in Parts A and B of Example 34, was treated as described in Part A of Example 36. Ethoxyacetyl chloride was used instead of methoxypropionyl chloride. Ethyl 5-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (6.0 g, 17 mmol) and ammonium acetate (15 g) were sealed in a high-pressure vessel and heated for four days at 110 °C and then allowed to cool to ambient temperature. Aqueous sodium hydroxide (10%) was added, and the mixture was then extracted with dichloromethane (3 x). The product crystallized from the dichloromethane and was collected in two crops to provide 2.64 g of 5-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide as an off-white solid, mp 157-158 °C.

Anal. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found: C, 65.99; H, 6.67; N, 17.08.

Part B

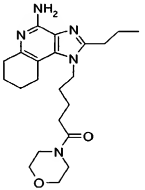
5-(2-Ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide (2.25 g, 6.89 mmol) was treated with mCPBA (2.77 g, 12.0 mmol), ammonium hydroxide (40 mL), and benzenesulfonyl chloride (1.71 mL, 13.4 mmol) according to the method described in Part D of Example 36. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 90:10 to 85:15). The

resulting product was triturated with 10% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide 0.752 g of 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide as a tan solid, mp 198-200 °C.

Anal. Calcd for $C_{18}H_{23}N_5O_2 \cdot 0.21\ H_2O$: C, 62.64; H, 6.84; N, 20.29. Found: C, 62.26; H, 6.80; N, 19.96.

Example 50

5-(4-Amino-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one

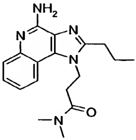


A mixture of 5-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one (1.66 g, 4.19 mmol, prepared in Example 34), platinum (IV) oxide (1.5 g, 6.6 mmol), and trifluoroacetic acid (25 mL) was placed in a Parr vessel and shaken under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) overnight. The reaction mixture was filtered through a layer of CELITE filter agent, and the filter cake was washed with ethanol. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluting with 95:5 dichloromethane:methanol). The resulting solid was triturated three times with 10% aqueous sodium hydroxide, isolated by filtration, and washed with water to provide 0.468 g of 5-(4-amino-2-propyl-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-morpholin-4-ylpentan-1-one as a white solid, mp 158-160 °C.

Anal. Calcd for $C_{22}H_{33}N_5O_2 \cdot 0.05\ H_2O$: C, 65.99; H, 8.33; N, 17.49. Found: C, 65.59; H, 8.60; N, 17.76.

Example 51

3-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N,N*-dimethylpropionamide



Part A

Dimethylamine (15 mL of a 40% aqueous solution) was added to a solution of ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (4.02 g, 12.9 mmol, prepared in Part B of Example 18) in THF (7 mL), and the reaction mixture was heated at 110 °C overnight in a pressure vessel. The reaction was allowed to cool to ambient temperature and concentrated under reduced pressure to provide 4.1 g of *N,N*-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide as a dark brown solid.

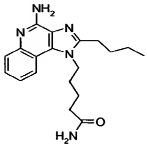
Part B

N,N-Dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide (2.40 g, 7.73 mmol) was treated with mCPBA (3.11 g, 13.5 mmol), ammonium hydroxide (40 mL), and benzenesulfonyl chloride (1.92 mL, 15.1 mmol) according to the method described in Part D of Example 36. The crude product was purified by column chromatography on silica gel (eluting with 93:7 dichloromethane:methanol) to provide 0.097 g of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N,N*-dimethylpropionamide as a tan powder, mp 207-209 °C.

Anal. Calcd for $C_{18}H_{23}N_5O \cdot 0.19\ H_2O$: C, 65.75; H, 7.07; N, 21.3. Found: C, 65.71; H, 7.38; N, 20.9.

Example 52

5-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide



Part A

Ethyl 5-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (10.0 g, 28.2 mmol, prepared in Example 46) and ammonium acetate (10 g) were sealed in a high-pressure vessel, heated for two days at 130 °C, and then allowed to cool to ambient temperature. Saturated aqueous sodium bicarbonate was added, and the mixture was then extracted with dichloromethane. The combined organic fractions were washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 8.6 g of 5-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide.

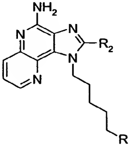
Part B

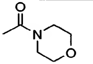
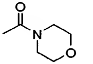
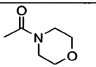
5-(2-Butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide (8.6 g, 26.5 mmol) was treated with mCPBA (10.7 g, 46.4 mmol), ammonium hydroxide (40 mL), and benzenesulfonyl chloride (6.59 mL, 51.6 mmol) according to the method described in Part D of Example 36. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 90:10 to 80:20). The resulting product was sonicated three times with 10% aqueous sodium hydroxide and once with 30% aqueous sodium hydroxide, isolated by filtration, washed with water, and dried overnight in a vacuum oven to provide 0.367 g of 5-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide as a tan solid, mp 219-221 °C.

Anal. Calcd for $C_{19}H_{25}N_5O \cdot 0.21\ H_2O$: C, 66.50; H, 7.46; N, 20.41. Found: C, 66.34; H, 7.81; N, 20.01.

Examples 53-58

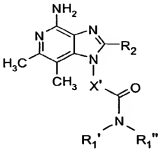
The methods described in Example 37, 38, and 39, using ethyl 6-aminocaproate hydrochloride instead of ethyl 4-aminobutyrate hydrochloride in Part A of Example 37, can be used to prepare Examples 53-58. Propionyl chloride can be used instead of butyryl chloride in Part C of Example 37 to prepare Examples 55 and 56.



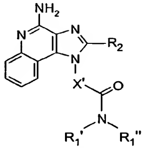
Example	R_2	R	name
53	$-CH_2CH_2CH_3$		6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylhexan-1-one
54	$-CH_2CH_2CH_3$	$-C(O)-NH_2$	6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide
55	$-CH_2CH_3$		6-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylhexan-1-one
56	$-CH_2CH_3$	$-C(O)-NH_2$	6-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide
57	$-CH_2OCH_2CH_3$		6-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1-morpholin-4-ylhexan-1-one
58	$-CH_2OCH_2CH_3$	$-C(O)-NH_2$	6-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)hexanamide

Exemplary Compounds

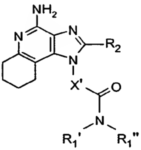
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIa, IVd, Vc, or VIb) and the following R_1', R_1'', X', and R_2 substituents, wherein each line of the table is matched with Formula IIIa, IVd, Vc, or VIb to represent a specific compound.



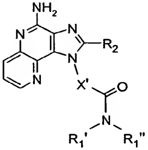
IIIa



IVd



Vc



VIb

R_1'	R_1''	X'	R_2
hydrogen	hydrogen	$-(CH_2)-$	methyl
hydrogen	hydrogen	$-(CH_2)-$	ethyl
hydrogen	hydrogen	$-(CH_2)-$	n-propyl
hydrogen	hydrogen	$-(CH_2)-$	n-butyl
hydrogen	hydrogen	$-(CH_2)-$	ethoxymethyl
hydrogen	hydrogen	$-(CH_2)-$	2-methoxyethyl
hydrogen	hydrogen	$-(CH_2)_2-$	methyl
hydrogen	hydrogen	$-(CH_2)_2-$	ethyl
hydrogen	hydrogen	$-(CH_2)_2-$	n-propyl
hydrogen	hydrogen	$-(CH_2)_2-$	n-butyl
hydrogen	hydrogen	$-(CH_2)_2-$	ethoxymethyl
hydrogen	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
hydrogen	hydrogen	$-(CH_2)_3-$	methyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethyl
hydrogen	hydrogen	$-(CH_2)_3-$	n-propyl
hydrogen	hydrogen	$-(CH_2)_3-$	n-butyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethoxymethyl

hydrogen	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2-$	methyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2-$	ethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2-$	n-propyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2-$	n-butyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2-$	ethoxymethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2-$	2-methoxyethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
hydrogen	methyl	$-(CH_2)-$	methyl
hydrogen	methyl	$-(CH_2)-$	ethyl
hydrogen	methyl	$-(CH_2)-$	n-propyl
hydrogen	methyl	$-(CH_2)-$	n-butyl
hydrogen	methyl	$-(CH_2)-$	ethoxymethyl
hydrogen	methyl	$-(CH_2)-$	2-methoxyethyl
hydrogen	methyl	$-(CH_2)_2-$	methyl
hydrogen	methyl	$-(CH_2)_2-$	ethyl
hydrogen	methyl	$-(CH_2)_2-$	n-propyl
hydrogen	methyl	$-(CH_2)_2-$	n-butyl
hydrogen	methyl	$-(CH_2)_2-$	ethoxymethyl
hydrogen	methyl	$-(CH_2)_2-$	2-methoxyethyl
hydrogen	methyl	$-(CH_2)_3-$	methyl
hydrogen	methyl	$-(CH_2)_3-$	ethyl
hydrogen	methyl	$-(CH_2)_3-$	n-propyl
hydrogen	methyl	$-(CH_2)_3-$	n-butyl
hydrogen	methyl	$-(CH_2)_3-$	ethoxymethyl
hydrogen	methyl	$-(CH_2)_3-$	2-methoxyethyl
hydrogen	methyl	$-CH_2C(CH_3)_2-$	methyl
hydrogen	methyl	$-CH_2C(CH_3)_2-$	ethyl
hydrogen	methyl	$-CH_2C(CH_3)_2-$	n-propyl
hydrogen	methyl	$-CH_2C(CH_3)_2-$	n-butyl
hydrogen	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
hydrogen	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
methyl	methyl	$-(CH_2)-$	methyl
methyl	methyl	$-(CH_2)-$	ethyl
methyl	methyl	$-(CH_2)-$	n-propyl
methyl	methyl	$-(CH_2)-$	n-butyl
methyl	methyl	$-(CH_2)-$	ethoxymethyl
methyl	methyl	$-(CH_2)-$	2-methoxyethyl
methyl	methyl	$-(CH_2)_2-$	methyl

methyl	methyl	$-(CH_2)_2-$	ethyl
methyl	methyl	$-(CH_2)_2-$	n-propyl
methyl	methyl	$-(CH_2)_2-$	n-butyl
methyl	methyl	$-(CH_2)_2-$	ethoxymethyl
methyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
methyl	methyl	$-(CH_2)_3-$	methyl
methyl	methyl	$-(CH_2)_3-$	ethyl
methyl	methyl	$-(CH_2)_3-$	n-propyl
methyl	methyl	$-(CH_2)_3-$	n-butyl
methyl	methyl	$-(CH_2)_3-$	ethoxymethyl
methyl	methyl	$-(CH_2)_3-$	2-methoxyethyl
methyl	methyl	$-CH_2C(CH_3)_2-$	methyl
methyl	methyl	$-CH_2C(CH_3)_2-$	ethyl
methyl	methyl	$-CH_2C(CH_3)_2-$	n-propyl
methyl	methyl	$-CH_2C(CH_3)_2-$	n-butyl
methyl	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
methyl	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
ethyl	hydrogen	$-(CH_2)-$	methyl
ethyl	hydrogen	$-(CH_2)-$	ethyl
ethyl	hydrogen	$-(CH_2)-$	n-propyl
ethyl	hydrogen	$-(CH_2)-$	n-butyl
ethyl	hydrogen	$-(CH_2)-$	ethoxymethyl
ethyl	hydrogen	$-(CH_2)-$	2-methoxyethyl
ethyl	hydrogen	$-(CH_2)_2-$	methyl
ethyl	hydrogen	$-(CH_2)_2-$	ethyl
ethyl	hydrogen	$-(CH_2)_2-$	n-propyl
ethyl	hydrogen	$-(CH_2)_2-$	n-butyl
ethyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
ethyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
ethyl	hydrogen	$-(CH_2)_3-$	methyl
ethyl	hydrogen	$-(CH_2)_3-$	ethyl
ethyl	hydrogen	$-(CH_2)_3-$	n-propyl
ethyl	hydrogen	$-(CH_2)_3-$	n-butyl
ethyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
ethyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	methyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	ethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	n-propyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	n-butyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	ethoxymethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2-$	2-methoxyethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl

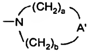
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
ethyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
ethyl	methyl	$-(CH_2)-$	methyl
ethyl	methyl	$-(CH_2)-$	ethyl
ethyl	methyl	$-(CH_2)-$	n-propyl
ethyl	methyl	$-(CH_2)-$	n-butyl
ethyl	methyl	$-(CH_2)-$	ethoxymethyl
ethyl	methyl	$-(CH_2)-$	2-methoxyethyl
ethyl	methyl	$-(CH_2)_2-$	methyl
ethyl	methyl	$-(CH_2)_2-$	ethyl
ethyl	methyl	$-(CH_2)_2-$	n-propyl
ethyl	methyl	$-(CH_2)_2-$	n-butyl
ethyl	methyl	$-(CH_2)_2-$	ethoxymethyl
ethyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
ethyl	methyl	$-(CH_2)_3-$	methyl
ethyl	methyl	$-(CH_2)_3-$	ethyl
ethyl	methyl	$-(CH_2)_3-$	n-propyl
ethyl	methyl	$-(CH_2)_3-$	n-butyl
ethyl	methyl	$-(CH_2)_3-$	ethoxymethyl
ethyl	methyl	$-(CH_2)_3-$	2-methoxyethyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	methyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	ethyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	n-propyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	n-butyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
ethyl	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
ethyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
n-propyl	hydrogen	$-(CH_2)-$	methyl
n-propyl	hydrogen	$-(CH_2)-$	ethyl
n-propyl	hydrogen	$-(CH_2)-$	n-propyl
n-propyl	hydrogen	$-(CH_2)-$	n-butyl
n-propyl	hydrogen	$-(CH_2)-$	ethoxymethyl
n-propyl	hydrogen	$-(CH_2)-$	2-methoxyethyl
n-propyl	hydrogen	$-(CH_2)_2-$	methyl
n-propyl	hydrogen	$-(CH_2)_2-$	ethyl
n-propyl	hydrogen	$-(CH_2)_2-$	n-propyl
n-propyl	hydrogen	$-(CH_2)_2-$	n-butyl
n-propyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
n-propyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
n-propyl	hydrogen	$-(CH_2)_3-$	methyl
n-propyl	hydrogen	$-(CH_2)_3-$	ethyl
n-propyl	hydrogen	$-(CH_2)_3-$	n-propyl
n-propyl	hydrogen	$-(CH_2)_3-$	n-butyl
n-propyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl

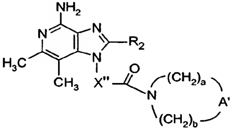
n-propyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2-$	methyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2-$	ethyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2-$	n-propyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2-$	n-butyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2-$	ethoxymethyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2-$	2-methoxyethyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
n-propyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
n-propyl	methyl	$-(CH_2)-$	methyl
n-propyl	methyl	$-(CH_2)-$	ethyl
n-propyl	methyl	$-(CH_2)-$	n-propyl
n-propyl	methyl	$-(CH_2)-$	n-butyl
n-propyl	methyl	$-(CH_2)-$	ethoxymethyl
n-propyl	methyl	$-(CH_2)-$	2-methoxyethyl
n-propyl	methyl	$-(CH_2)_2-$	methyl
n-propyl	methyl	$-(CH_2)_2-$	ethyl
n-propyl	methyl	$-(CH_2)_2-$	n-propyl
n-propyl	methyl	$-(CH_2)_2-$	n-butyl
n-propyl	methyl	$-(CH_2)_2-$	ethoxymethyl
n-propyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
n-propyl	methyl	$-(CH_2)_3-$	methyl
n-propyl	methyl	$-(CH_2)_3-$	ethyl
n-propyl	methyl	$-(CH_2)_3-$	n-propyl
n-propyl	methyl	$-(CH_2)_3-$	n-butyl
n-propyl	methyl	$-(CH_2)_3-$	ethoxymethyl
n-propyl	methyl	$-(CH_2)_3-$	2-methoxyethyl
n-propyl	methyl	$-CH_2C(CH_3)_2-$	methyl
n-propyl	methyl	$-CH_2C(CH_3)_2-$	ethyl
n-propyl	methyl	$-CH_2C(CH_3)_2-$	n-propyl
n-propyl	methyl	$-CH_2C(CH_3)_2-$	n-butyl
n-propyl	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
n-propyl	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
n-propyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
n-butyl	hydrogen	$-(CH_2)-$	methyl
n-butyl	hydrogen	$-(CH_2)-$	ethyl
n-butyl	hydrogen	$-(CH_2)-$	n-propyl
n-butyl	hydrogen	$-(CH_2)-$	n-butyl
n-butyl	hydrogen	$-(CH_2)-$	ethoxymethyl
n-butyl	hydrogen	$-(CH_2)-$	2-methoxyethyl
n-butyl	hydrogen	$-(CH_2)_2-$	methyl

n-butyl	hydrogen	$-(CH_2)_2-$	ethyl
n-butyl	hydrogen	$-(CH_2)_2-$	n-propyl
n-butyl	hydrogen	$-(CH_2)_2-$	n-butyl
n-butyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
n-butyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
n-butyl	hydrogen	$-(CH_2)_3-$	methyl
n-butyl	hydrogen	$-(CH_2)_3-$	ethyl
n-butyl	hydrogen	$-(CH_2)_3-$	n-propyl
n-butyl	hydrogen	$-(CH_2)_3-$	n-butyl
n-butyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
n-butyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	methyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	ethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	n-propyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	n-butyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	ethoxymethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2-$	2-methoxyethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
n-butyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
n-butyl	methyl	$-(CH_2)-$	methyl
n-butyl	methyl	$-(CH_2)-$	ethyl
n-butyl	methyl	$-(CH_2)-$	n-propyl
n-butyl	methyl	$-(CH_2)-$	n-butyl
n-butyl	methyl	$-(CH_2)-$	ethoxymethyl
n-butyl	methyl	$-(CH_2)-$	2-methoxyethyl
n-butyl	methyl	$-(CH_2)_2-$	methyl
n-butyl	methyl	$-(CH_2)_2-$	ethyl
n-butyl	methyl	$-(CH_2)_2-$	n-propyl
n-butyl	methyl	$-(CH_2)_2-$	n-butyl
n-butyl	methyl	$-(CH_2)_2-$	ethoxymethyl
n-butyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
n-butyl	methyl	$-(CH_2)_3-$	methyl
n-butyl	methyl	$-(CH_2)_3-$	ethyl
n-butyl	methyl	$-(CH_2)_3-$	n-propyl
n-butyl	methyl	$-(CH_2)_3-$	n-butyl
n-butyl	methyl	$-(CH_2)_3-$	ethoxymethyl
n-butyl	methyl	$-(CH_2)_3-$	2-methoxyethyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	methyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	ethyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	n-propyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	n-butyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
n-butyl	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl

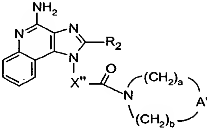
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
n-butyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
phenyl	hydrogen	$-(CH_2)-$	methyl
phenyl	hydrogen	$-(CH_2)-$	ethyl
phenyl	hydrogen	$-(CH_2)-$	n-propyl
phenyl	hydrogen	$-(CH_2)-$	n-butyl
phenyl	hydrogen	$-(CH_2)-$	ethoxymethyl
phenyl	hydrogen	$-(CH_2)-$	2-methoxyethyl
phenyl	hydrogen	$-(CH_2)_2-$	methyl
phenyl	hydrogen	$-(CH_2)_2-$	ethyl
phenyl	hydrogen	$-(CH_2)_2-$	n-propyl
phenyl	hydrogen	$-(CH_2)_2-$	n-butyl
phenyl	hydrogen	$-(CH_2)_2-$	ethoxymethyl
phenyl	hydrogen	$-(CH_2)_2-$	2-methoxyethyl
phenyl	hydrogen	$-(CH_2)_3-$	methyl
phenyl	hydrogen	$-(CH_2)_3-$	ethyl
phenyl	hydrogen	$-(CH_2)_3-$	n-propyl
phenyl	hydrogen	$-(CH_2)_3-$	n-butyl
phenyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
phenyl	hydrogen	$-(CH_2)_3-$	2-methoxyethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	methyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	ethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	n-propyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	n-butyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	ethoxymethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2-$	2-methoxyethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	methyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-propyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	n-butyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
phenyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
phenyl	methyl	$-(CH_2)-$	methyl
phenyl	methyl	$-(CH_2)-$	ethyl
phenyl	methyl	$-(CH_2)-$	n-propyl
phenyl	methyl	$-(CH_2)-$	n-butyl
phenyl	methyl	$-(CH_2)-$	ethoxymethyl
phenyl	methyl	$-(CH_2)-$	2-methoxyethyl
phenyl	methyl	$-(CH_2)_2-$	methyl
phenyl	methyl	$-(CH_2)_2-$	ethyl
phenyl	methyl	$-(CH_2)_2-$	n-propyl
phenyl	methyl	$-(CH_2)_2-$	n-butyl
phenyl	methyl	$-(CH_2)_2-$	ethoxymethyl
phenyl	methyl	$-(CH_2)_2-$	2-methoxyethyl
phenyl	methyl	$-(CH_2)_3-$	methyl
phenyl	methyl	$-(CH_2)_3-$	ethyl
phenyl	methyl	$-(CH_2)_3-$	n-propyl
phenyl	methyl	$-(CH_2)_3-$	n-butyl
phenyl	methyl	$-(CH_2)_3-$	ethoxymethyl

phenyl	methyl	$-(CH_2)_3-$	2-methoxyethyl
phenyl	methyl	$-CH_2C(CH_3)_2-$	methyl
phenyl	methyl	$-CH_2C(CH_3)_2-$	ethyl
phenyl	methyl	$-CH_2C(CH_3)_2-$	n-propyl
phenyl	methyl	$-CH_2C(CH_3)_2-$	n-butyl
phenyl	methyl	$-CH_2C(CH_3)_2-$	ethoxymethyl
phenyl	methyl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
phenyl	methyl	$-CH_2C(CH_3)_2CH_2-$	methyl
phenyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
phenyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
phenyl	methyl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
phenyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
phenyl	methyl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl

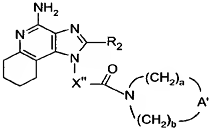
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIb, IVe, Vd, or VIc) and the following , X", and R_2 substituents, wherein each line of the table is matched with Formula IIIb, IVe, Vd, or VIc to represent a specific compound.



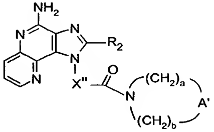
IIIb



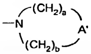
IVe



Vd



VIc

	X"	R_2
pyrrolidin-1-yl	$-(CH_2)-$	methyl

pyrrolidin-1-yl	$-(CH_2)-$	ethyl
pyrrolidin-1-yl	$-(CH_2)-$	n-propyl
pyrrolidin-1-yl	$-(CH_2)-$	n-butyl
pyrrolidin-1-yl	$-(CH_2)-$	ethoxymethyl
pyrrolidin-1-yl	$-(CH_2)-$	2-methoxyethyl
pyrrolidin-1-yl	$-(CH_2)_2-$	methyl
pyrrolidin-1-yl	$-(CH_2)_2-$	ethyl
pyrrolidin-1-yl	$-(CH_2)_2-$	n-propyl
pyrrolidin-1-yl	$-(CH_2)_2-$	n-butyl
pyrrolidin-1-yl	$-(CH_2)_2-$	ethoxymethyl
pyrrolidin-1-yl	$-(CH_2)_2-$	2-methoxyethyl
pyrrolidin-1-yl	$-(CH_2)_3-$	methyl
pyrrolidin-1-yl	$-(CH_2)_3-$	ethyl
pyrrolidin-1-yl	$-(CH_2)_3-$	n-propyl
pyrrolidin-1-yl	$-(CH_2)_3-$	n-butyl
pyrrolidin-1-yl	$-(CH_2)_3-$	ethoxymethyl
pyrrolidin-1-yl	$-(CH_2)_3-$	2-methoxyethyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2-$	methyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2-$	ethyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2-$	n-propyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2-$	n-butyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	methyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
pyrrolidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
piperidin-1-yl	$-(CH_2)-$	methyl
piperidin-1-yl	$-(CH_2)-$	ethyl
piperidin-1-yl	$-(CH_2)-$	n-propyl
piperidin-1-yl	$-(CH_2)-$	n-butyl
piperidin-1-yl	$-(CH_2)-$	ethoxymethyl
piperidin-1-yl	$-(CH_2)-$	2-methoxyethyl
piperidin-1-yl	$-(CH_2)_2-$	methyl
piperidin-1-yl	$-(CH_2)_2-$	ethyl
piperidin-1-yl	$-(CH_2)_2-$	n-propyl
piperidin-1-yl	$-(CH_2)_2-$	n-butyl
piperidin-1-yl	$-(CH_2)_2-$	ethoxymethyl
piperidin-1-yl	$-(CH_2)_2-$	2-methoxyethyl
piperidin-1-yl	$-(CH_2)_3-$	methyl
piperidin-1-yl	$-(CH_2)_3-$	ethyl
piperidin-1-yl	$-(CH_2)_3-$	n-propyl
piperidin-1-yl	$-(CH_2)_3-$	n-butyl
piperidin-1-yl	$-(CH_2)_3-$	ethoxymethyl
piperidin-1-yl	$-(CH_2)_3-$	2-methoxyethyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	methyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	ethyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	n-propyl

piperidin-1-yl	$-CH_2C(CH_3)_2-$	n-butyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
piperidin-1-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	methyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
piperidin-1-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	methyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	ethyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	n-propyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	n-butyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-(CH_2)-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	methyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	ethyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	n-propyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	n-butyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-(CH_2)_2-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	methyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	ethyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	n-propyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	n-butyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-(CH_2)_3-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	methyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	ethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	n-propyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	n-butyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	methyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
4-acetylpiperazin-1-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
morpholin-4-yl	$-(CH_2)-$	methyl
morpholin-4-yl	$-(CH_2)-$	ethyl
morpholin-4-yl	$-(CH_2)-$	n-propyl
morpholin-4-yl	$-(CH_2)-$	n-butyl
morpholin-4-yl	$-(CH_2)-$	ethoxymethyl
morpholin-4-yl	$-(CH_2)-$	2-methoxyethyl
morpholin-4-yl	$-(CH_2)_2-$	methyl
morpholin-4-yl	$-(CH_2)_2-$	ethyl
morpholin-4-yl	$-(CH_2)_2-$	n-propyl
morpholin-4-yl	$-(CH_2)_2-$	n-butyl
morpholin-4-yl	$-(CH_2)_2-$	ethoxymethyl

morpholin-4-yl	$-(CH_2)_2-$	2-methoxyethyl
morpholin-4-yl	$-(CH_2)_3-$	methyl
morpholin-4-yl	$-(CH_2)_3-$	ethyl
morpholin-4-yl	$-(CH_2)_3-$	n-propyl
morpholin-4-yl	$-(CH_2)_3-$	n-butyl
morpholin-4-yl	$-(CH_2)_3-$	ethoxymethyl
morpholin-4-yl	$-(CH_2)_3-$	2-methoxyethyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	methyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	ethyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	n-propyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	n-butyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
morpholin-4-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	methyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
morpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	methyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	methyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_2-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	methyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-(CH_2)_3-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	methyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2-$	2-methoxyethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	methyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	ethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	n-propyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	n-butyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
1,1-dioxothiomorpholin-4-yl	$-CH_2C(CH_3)_2CH_2-$	2-methoxyethyl

CYTOKINE INDUCTION IN HUMAN CELLS

Many compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α in human cells when tested using the method described below. Particular examples include but are not limited to the compounds of Examples 1-52.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 µM.

Incubation

The solution of test compound is added at 60 µM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the

desired range (30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (~200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

TNF-α INHIBITION IN MOUSE CELLS

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below.

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor-α (TNF-α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3 x 10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 μL) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3 x 10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by a dose response assay.

Incubation

A solution of test compound (1μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μL) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA).

The final concentration of cells is 1 x 10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

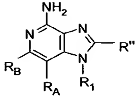
Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and

embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):

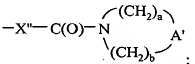


I

wherein:

R_1 is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

each R_a is independently selected from the group consisting of:

halogen,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

each R_b is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

each R_c is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_6 is independently selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl; and

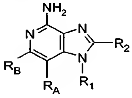
R" is hydrogen or a non-interfering substituent;

with the proviso that when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be -X"-C(O)-N(R_1')(R_1");

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein the compound or salt induces the biosynthesis of one or more cytokines.

3. A compound of the formula (II):

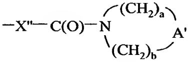


II

wherein:

R_1 is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and

$-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R_a groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_c groups;

or R_A and R_B taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups;

each R_a is independently selected from the group consisting of:

halogen,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

each R_b is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

each R_c is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

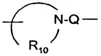
-O-C(O)-O-,

$-N(R_8)-Q-$,

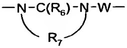
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

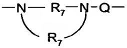
$-C(R_6)-N(OR_9)-$,



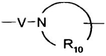
,



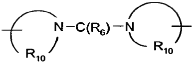
,



,



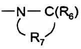
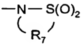
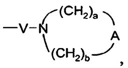
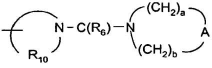
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

 ,  ,  , and  ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

with the proviso that when R_A and R_B form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R_b groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R_c groups, then R_1 can also be $-X''-C(O)-N(R_1')(R_1'')$;

or a pharmaceutically acceptable salt thereof.

4. The compound or salt of claim 3 wherein X' is $-CH_2-C_{0-10}$ alkylene- or X'' is $-CH_2-C_{0-10}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

5. The compound or salt of claim 3 wherein A' is -O- or $-N(Q-R_4)-$, and a and b are independently integers from 2 to 3; or A' is $-CH_2-$, and a and b are independently integers from 1 to 3.

6. The compound or salt of claim 3 wherein R_1' is hydrogen or C_{1-3} alkyl.

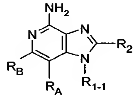
7. The compound or salt of claim 3 wherein R_1'' is hydrogen.

8. The compound or salt of claim 3 wherein R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

9. The compound or salt of claim 8 wherein R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl.

10. The compound or salt of claim 3 wherein the fused aryl ring, fused heteroaryl ring, fused 5 to 7 membered saturated ring, or fused 5 to 7 membered saturated ring containing one N or S atom is unsubstituted.

11. A compound of the formula (III):

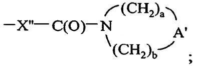


III

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and

-X-R_5;

X is in selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

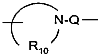
-O-C(O)-O-,

-$N(R_8)$-Q-,

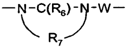
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

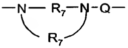
-$C(R_6)$-$N(OR_9)$-,



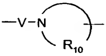
,



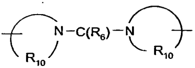
,



,



, and

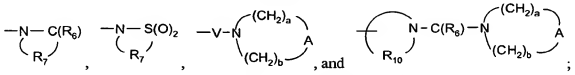


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl

wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

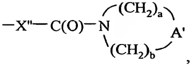
each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

12. The compound or salt of claim 11 wherein X' is $-CH_2-C_{0-4}$ alkylene- or X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

13. The compound or salt of claim 12 wherein X' is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, or $-CH_2C(CH_3)_2CH_2-$; or X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

14. The compound or salt of claim 11 wherein R_{1-1} is



, A' is -O-, and a and b are each 2.

15. The compound or salt of claim 11 wherein R_1' is hydrogen or C_{1-3} alkyl, and R_1'' is hydrogen.

16. The compound or salt of claim 11 wherein R_1' and R_1'' are hydrogen.

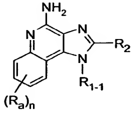
17. The compound or salt of claim 11 wherein R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

18. The compound or salt of claim 17 wherein R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl.

19. The compound or salt of claim 18 wherein R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

20. The compound or salt of claim 11 wherein R_A and R_B are methyl.

21. A compound of the formula (IV):

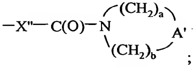


IV

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_a is independently selected from the group consisting of:

halogen,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

n is an integer of 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

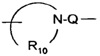
-O-C(O)-O-,

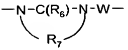
-N(R_8)-Q-,

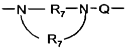
-C(R_6)-N(R_8)-,

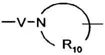
-O-C(R_6)-N(R_8)-,

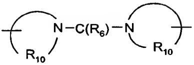
-C(R_6)-N(OR_9)-,


,


,

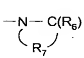
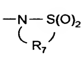
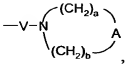
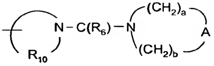

,


, and


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


,

,

, and

;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

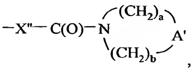
each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

22. The compound or salt of claim 21 wherein X' is $-CH_2-C_{0-4}$ alkylene- or X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

23. The compound or salt of claim 22 wherein X' is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, or $-CH_2C(CH_3)_2CH_2-$; or X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

24. The compound or salt of claim 21 wherein R_{1-1} is



, A' is -O-, and a and b are each 2.

25. The compound or salt of claim 21 wherein R_1' is hydrogen or C_{1-3} alkyl, and R_1" is hydrogen.

26. The compound or salt of claim 21 wherein R_1' and R_1" are hydrogen.

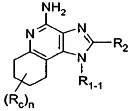
27. The compound or salt of claim 21 wherein R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X-R_4, or -X-Y-R_4; X is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, or -C(R_6)-N(OR_9)-; and R_4 is alkyl.

28. The compound or salt of claim 27 wherein R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl.

29. The compound or salt of claim 28 wherein R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

30. The compound or salt of claim 21 wherein n is 0.

31. A compound of the formula (V):

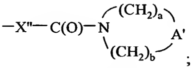


V

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_c is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

n is an integer of 0 to 4;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

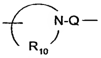
-O-C(O)-O-,

-N(R_8)-Q-,

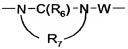
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

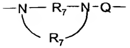
-C(R_6)-N(OR_9)-,

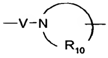


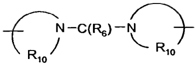
,



,

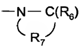
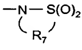
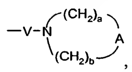
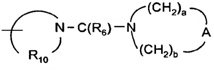

,


, and


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


,

,

, and

;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$,

$-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

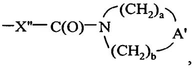
each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

32. The compound or salt of claim 31 wherein X' is $-CH_2-C_{0-4}$ alkylene- or X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

33. The compound or salt of claim 32 wherein X' is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, or $-CH_2C(CH_3)_2CH_2-$; or X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

34. The compound or salt of claim 31 wherein R_{1-1} is



, A' is -O-, and a and b are each 2.

35. The compound or salt of claim 31 wherein R_1' is hydrogen or C_{1-3} alkyl, and R_1" is hydrogen.

36. The compound or salt of claim 31 wherein R_1' and R_1" are hydrogen.

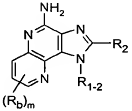
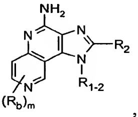
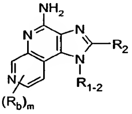
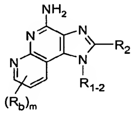
37. The compound or salt of claim 31 wherein R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

38. The compound or salt of claim 37 wherein R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl.

39. The compound or salt of claim 38 wherein R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

40. The compound or salt of claim 31 wherein n is 0.

41. A compound selected from the group consisting of the formulas (VI, VII, VIII, and IX):


,

,

, and


VI VII VIII IX

wherein:

R_{1-2} is selected from the group consisting of:

-X"-C(O)-N(R_1')(R_1") and

$$-X''-C(O)-N\begin{matrix}\diagup(CH_2)_a\diagdown \\ \qquad\qquad A' \\ \diagdown(CH_2)_b\diagup\end{matrix}\ ;$$

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_b is independently selected from the group consisting of:

halogen,
hydroxy,
alkyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$;

m is an integer of 0 to 3;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

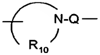
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

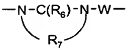
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

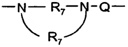
$-C(R_6)-N(OR_9)-$,



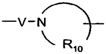
,



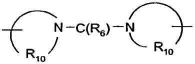
,



,



, and

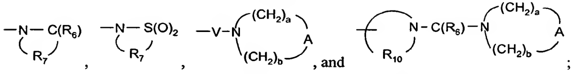


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl

wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, -CH$_2$-, and -N(R$_4$)-;

each Q is independently selected from the group consisting of a bond, -C(R$_6$)-, -C(R$_6$)-C(R$_6$)-, -S(O)$_2$-, -C(R$_6$)-N(R$_8$)-W-, -S(O)$_2$-N(R$_8$)-, -C(R$_6$)-O-, and -C(R$_6$)-N(OR$_9$)-;

V is selected from the group consisting of -C(R$_6$)-, -O-C(R$_6$)-, -N(R$_8$)-C(R$_6$)-, and -S(O)$_2$-; and

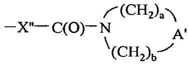
each W is independently selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;

or a pharmaceutically acceptable salt thereof.

42. The compound or salt of claim 41 wherein X" is -CH$_2$-C$_{0-4}$ alkylene- or -CH$_2$-C$_{1-4}$ alkylene-O-C$_{1-4}$ alkylene-.

43. The compound or salt of claim 42 wherein X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

44. The compound or salt of claim 41 wherein R_{1-2} is



, A' is -O-, and a and b are each 2.

45. The compound or salt of claim 41 wherein R_1' is hydrogen or C_{1-3} alkyl, and R_1'' is hydrogen.

46. The compound or salt of claim 41 wherein R_1' and R_1'' are hydrogen.

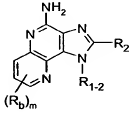
47. The compound or salt of claim 41 wherein R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

48. The compound or salt of claim 47 wherein R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl.

49. The compound or salt of claim 48 wherein R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

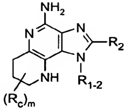
50. The compound or salt of claim 41 wherein m is 0.

51. The compound or salt of claim 41 wherein the compound is of the following formula (VI):



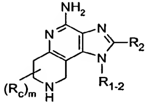
VI.

52. A compound selected from the group consisting of the formulas (X, XI, XII, and XIII):



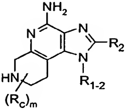
X

,



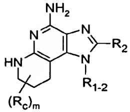
XI

,



XII

, and

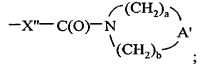


XIII

wherein:

R_{1-2} is selected from the group consisting of:

-X"-C(O)-N(R_1')(R_1") and



;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_c is independently selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

m is an integer of 0 to 3;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

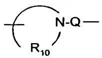
-O-C(O)-O-,

-N(R_8)-Q-,

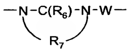
-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

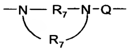
-C(R_6)-N(OR_9)-,



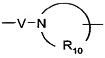
,



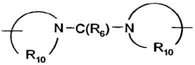
,



,



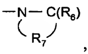
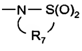
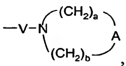
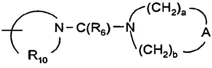
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

 ,  ,  , and  ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, -CH$_2$-, and -N(R_4)-;

each Q is independently selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

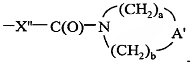
each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

53. The compound or salt of claim 52 wherein X" is $-CH_2-C_{0-4}$ alkylene- or $-CH_2-C_{1-4}$ alkylene-O-C_{1-4} alkylene-.

54. The compound or salt of claim 53 wherein X" is $-(CH_2)_{1-5}-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, or $-(CH_2)_3-O-CH_2-$.

55. The compound or salt of claim 52 wherein R_{1-2} is



, A' is -O-, and a and b are each 2.

56. The compound or salt of claim 52 wherein R_1' is hydrogen or C_{1-3} alkyl, and R_1" is hydrogen.

57. The compound or salt of claim 52 wherein R_1' and R_1" are hydrogen.

58. The compound or salt of claim 52 wherein R_2 is hydrogen, alkoxyalkylenyl, $-R_4$, $-X-R_4$, or $-X-Y-R_4$; X is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

59. The compound or salt of claim 58 wherein R_2 is hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl-O-C_{1-4} alkylenyl.

60. The compound or salt of claim 59 wherein R_2 is hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, or ethoxymethyl.

61. The compound or salt of claim 52 wherein m is 0.

62. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 1 and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 3 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 11 and a pharmaceutically acceptable carrier.

65. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 21 and a pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 31 and a pharmaceutically acceptable carrier.

67. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 41 and a pharmaceutically acceptable carrier.

68. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of claim 52 and a pharmaceutically acceptable carrier.

69. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 1 to the animal.

70. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 3 to the animal.

71. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 11 to the animal.

72. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 21 to the animal.

73. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 31 to the animal.

74. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 41 to the animal.

75. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 52 to the animal.

76. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 1 to the animal.

77. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 3 to the animal.

78. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 11 to the animal.

79. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 21 to the animal.

80. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 31 to the animal.

81. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 41 to the animal.

82. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 52 to the animal.

83. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 1 to the animal.

84. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 3 to the animal.

85. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 11 to the animal.

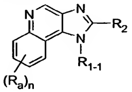
86. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 21 to the animal.

87. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 31 to the animal.

88. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 41 to the animal.

89. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 52 to the animal.

90. A compound of the formula (XIV):

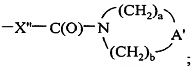


XIV

wherein:

R_{1-1} is selected from the group consisting of:

-X'-C(O)-N(R_1')(R_1") and



;

X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_a is independently selected from the group consisting of:

halogen,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

n is an integer of 0 to 4;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

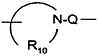
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

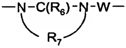
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

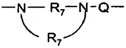
$-C(R_6)-N(OR_9)-$,



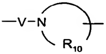
,



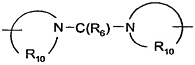
,



,



, and

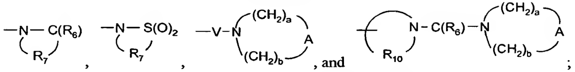


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl,

heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

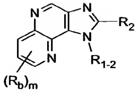
each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

91. A compound of the formula (XV):

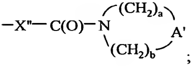


XV

wherein:

R_{1-2} is selected from the group consisting of:

$-X''-C(O)-N(R_1')(R_1'')$ and



;

X" is selected from the group consisting of $-CH(R_9)-$, $-CH(R_9)$-alkylene-, and $-CH(R_9)$-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1'' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,
halogen,
cyano,
nitro,
amino,
alkylamino,
dialkylamino,
arylsulfonyl, and
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

each R_b is independently selected from the group consisting of:

halogen,
hydroxy,
alkyl,
haloalkyl,
alkoxy, and
$-N(R_9)_2$;

m is an integer of 0 to 3;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

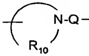
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

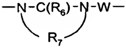
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

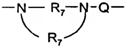
$-C(R_6)-N(OR_9)-$,



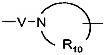
,



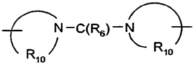
,



,



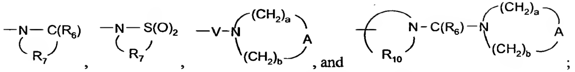
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

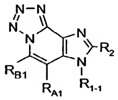
each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

92. A compound of the formula (XVI):

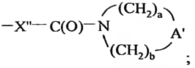


XVI

wherein:

R_{1-1} is selected from the group consisting of:

$-X'-C(O)-N(R_1')(R_1'')$ and



X' is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-;

X" is selected from the group consisting of -CH(R_9)-, -CH(R_9)-alkylene-, and -CH(R_9)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R_1' and R_1" are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

haloalkoxy,

halogen,

cyano,

nitro,

amino,

alkylamino,

dialkylamino,

arylsulfonyl, and

alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_{A1} and R_{B1} are independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

X is in selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

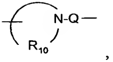
-O-C(O)-O-.

$-N(R_8)-Q-$,

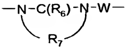
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

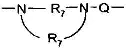
$-C(R_6)-N(OR_9)-$,



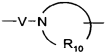
,



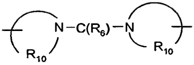
,



,



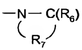
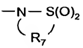
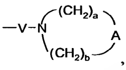
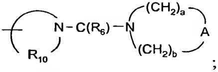
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

 ,  ,  , and  ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

or a pharmaceutically acceptable salt thereof.

AMIDE SUBSTITUED IMIDAZOPYRIDINES, IMIDAZOQUINOLINES, AND IMIDAZONAPHTHYRIDINES

ABSTRACT

Imidazopyridine, imidazoquinoline, and imidazonaphthyridine compounds having an amide substituent at the 1-position, pharmaceutical compositions containing the compounds, intermediates, and methods of making and methods of use of these compounds as immunomodulators, for modulating cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.